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CONTENTS OF PREVIOUS NUMBER

JULY 1943. NUMBER 1

Pathogenetic Mechanisms in Hemolytic Anemias. William Dameshek, M.D., Boston, and Captain Edward B. Miller, Medical Corps, Army of the United States.

Clinical Manifestations of Weil's Disease with Particular Reference to Meningitis. Muir Clapper, M.D., and Gordon B. Myers, M.D., Detroit.

Pentosuria Associated with Diabetes Mellitus. Morton H. Edelman, M.D., and Miriam Reiner, M.S., New York.

Clinical Experience with Mixtures of Protamine Zinc and Unmodified Insulins: A Preliminary Report. Alice G. Hildebrand, M.D., and Edward H. Rynearson, M.D., Rochester, Minn.

In Situ Effects of Antacids in Duodenal Ulcer. Captain J. Edward Berk, Medical Corps, Army of the United States, and Martin E. Rehfuss, M.D., and J. Earl Thomas, M.D., Philadelphia.

Symptoms and Incidence of Anemia in Hernia at the Esophageal Hiatus. William P. Murphy, M.D., Boston, and Major William E. Hay, Medical Corps, Army of the United States.

Association of Cirrhosis, Thrombopenia and Hemorrhagic Tendency. Carl G. Morlock, M.D., and Byron E. Hall, M.D., Rochester, Minn.

Studies in Syphilis: I. Review of the Incidence of Syphilis in Autopsies on Adults. Paul D. Rosahn, M.D., New Britain, Conn., and Bernard Black-Schaffer, M.D., Richmond, Va.

Nitrogen Equilibrium and Regeneration of Serum Protein Following Intravenous Use of Amino Acids. William J. Messinger, M.D., New York.

Tricuspid Stenosis: Incidence and Diagnosis. Curtis F. Garvin, M.D., Cleveland.

Cholesterol Content of the Urine in Patients with Cancer. Maurice Bruger, M.D., New York, with the Technical Assistance of Sylvia B. Ehrlich, B.S.

Progress in Internal Medicine:

Blood: A Review of the Recent Literature (To Be Concluded). Frank H. Bethell, M.D.; Cyrus C. Sturgis, M.D.; Robert A. Hettig, M.D., and Otto Tod Mallery Jr., M.D., Ann Arbor, Mich.

Book Reviews.

ARCHIVES of INTERNAL MEDICINE

VOLUME 72 AUGUST 1943 NUMBER 2

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CARRIÓN'S DISEASE

IMMUNOLOGIC STUDIES

CALDERON HOWE, M.D.

BOSTON

Carrión's disease is the name applied to the clinical disease entity caused by infection with Bartonella bacilliformis. The term includes both the severe anemic stage of the disease, Oroya fever, and the less severe eruptive stage, verruga peruana. In the regions where the disease is prevalent the term *la verruga* is used to indicate any form it may assume.

Many aspects of Carrión's disease in its various phases remain to be explained. Noteworthy among these is the immunologic sequence occurring in a human being during the course of infection. That a tangible immunologic response in the form of agglutinins does occur in some instances has already been demonstrated.[1] It has been the primary purpose of the present investigation further to define the limits of this immunologic response in relation to the course of the disease and to attempt to ascertain what part, if any, the presence of specific agglutinins may have in the long-standing acquired immunity which almost invariably follows infection.

It became evident that a possible approach to this problem might lie in determining by means of the agglutination test the level of humoral antibodies in the serum from a significant number of residents of regions where Carrión's disease is endemic. This group of subjects would of necessity have to include patients in all stages of this specific disease, with and without a past history of it.

A program of investigation has consequently been carried out in the regions near Lima, Peru, where Carrión's disease is endemic. The field work was confined solely to the valleys of the Santa Eulalia and Rimac rivers, most of the material coming from the valley of the former. The actual localities involved are indicated in figure 1. In addition to those patients studied in the field, a number were seen in various hospitals in Lima who had contracted their disease in endemic areas other than those already mentioned, thus broadening somewhat the scope of the clinical material.

It should be emphasized that even short residence in any of the endemic areas involves repeated exposure to infection, provided no steps are taken toward protection against the wild sandfly, which feeds on human beings and animals only at night. Of the three species of sandfly occurring in the verruga zones, namely, Phlebotomus noguchi, Phlebotomus peruensis and Phlebotomus verrucarum, the last-named is most probably the chief transmitter of the disease. Complete protection can be assured only by quitting before nightfall the rather narrow belt between about 800 and 3,000 meters above sea level where Phlebotomus occurs.

This investigation was financed in part from the Repayments Fund of the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School.

From the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, Boston, and the National Institute of Hygiene and Public Health, Lima, Peru.

1. Howe, C.: J. Exper. Med. **75**:65-75, 1942.

Occasional persons have contracted severe Oroya fever from even a single night's sojourn in these regions.[2] It is thus obvious that all of the persons encountered in the present study had had definite and sometimes prolonged exposure to infection with B. bacilliformis.

MATERIAL AND METHOD

A total of 203 residents of the endemic regions already mentioned were seen in the course of the present work. Included among them were persons with mild and with severe active Carrión's disease, in each of its several manifestations. A large part of them represented recent arrivals in the particular areas studied, the duration of their sojourn having been a matter of months or weeks, rather than years. Most of them were laborers on a new electric power project in the upper part of the Santa Eulalia river valley, still within the limits of the endemic area. All three species of sandfly occur in these localities, which are thus well

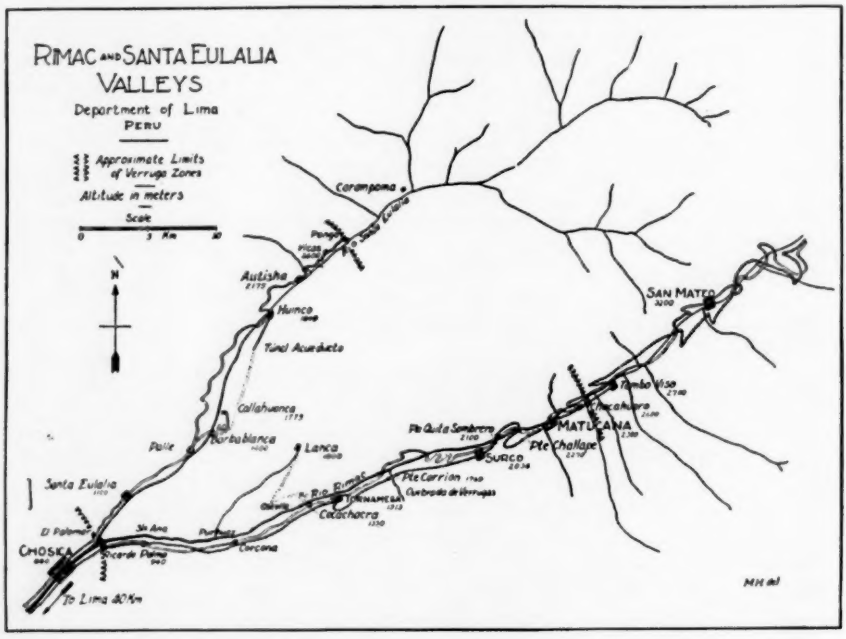

Fig. 1.—The area near Lima where the investigation reported here was carried out (from Hertig, M.: Am. J. Trop. Med. [supp.] **22**:1, 1942).

known centers of Carrión's disease. The remainder of the persons seen were longer term residents or natives of the two valleys mentioned and thus inevitably would have had prolonged exposure to infection.

Blood cultures were made for each patient, 5 to 6 drops of blood being inoculated directly into each of two tubes of Geiman tryptone semisolid bartonella medium.[3] This medium was used exclusively during the field work, since it has proved itself to be far superior to leptospira medium both for primary isolation and for maintenance of B. bacilliformis in the laboratory. Blood for serum was taken at the same time from each patient. The level of hemoglobin was determined by the method of Sahli, the results being checked from time to time with ones obtained with an electric photocolorimeter. The erythrocyte count, leukocyte count and hematocrit reading were determined when indicated, and a blood film was stained for B.

2. Hertig, M.: Am. J. Trop. Med. (supp.) **22**:4-5, 1942.
3. Geiman, Q. M.: Proc. Soc. Exper. Biol. & Med. **47**:329, 1941.

bacilliformis with Giemsa's solution. Relevant clinical information was obtained in every case, with special emphasis on any past history of Carrión's disease, previous residence in endemic regions and possible evidence of actual infection. A physical examination was done whenever indicated, special note being made of the type and extent of any verrucous eruption.

The blood cultures were kept in the laboratory at room temperature (28 ± 2 C.) and examined with a binocular microscope (low power) after ten days to two weeks of incubation. At the end of this time in the tubes showing growth of B. bacilliformis the typical pearly white granular colonies were detectable in the strands of fibrin remaining from the original blood clot. All strains isolated from blood cultures were confirmed by dark field examination, were subcultured and have been carried through at least four transfers. They have also in many cases been transferred to Geiman blood agar[3] for determination of motility by dark field examination and for further morphologic and immunologic studies now in progress.

An agglutination test with B. bacilliformis was performed on serum from every patient within a period of not more than two weeks after the date on which the blood was taken. The antigen used had been prepared in Boston from stock laboratory cultures which had been maintained on Geiman blood agar. These cultures had originated from four different sources, as follows:

The first strain was isolated from the proboscis of a wild sandfly in 1939 in Peru by Dr. Marshall Hertig. The second originated from a patient with Oroya fever in Peru and was obtained by Dr. Q. M. Geiman in 1939. The third was isolated from a patient with severe Oroya fever in Colombia in 1940 and was obtained by Dr. José Jiménez Franco, of Lima. The fourth, from a patient with severe Oroya fever in Peru, I isolated myself in 1940. The reasons for the use of the four different strains in making up the antigen will be discussed later.

The antigen, as used, consisted of five days' growth of these four strains on Geiman blood agar. The organisms were washed off the slants, centrifuged and resuspended in a 0.4 per cent concentration of solution of formaldehyde U. S. P. in 0.85 per cent solution of sodium chloride, standardized to represent the growth of one slant per cubic centimeter of suspending medium.

The agglutination test has thus been modified by the substitution of a formaldehyde-treated antigen for the suspension of living organisms which was used in the test as originally devised. Formaldehyde treatment of the suspension was introduced at first chiefly as a measure of convenience, since it was felt that a well preserved and standardized antigen would give more consistent results. But it also afforded some coincidental observations of interest, which in retrospect substantiate the greater value of this type of antigen in testing unknown human serums.

In the original experiments,[1] in which suspensions of living organisms were agglutinated by serum of rabbits immunized with living organisms, the flocculus was coarse, heavy and tightly cohesive. Under the dark field microscope the large flakes of clumped organisms were easily demonstrated. In testing the agglutinating titer of immune rabbit serums used for therapeutic purposes during the present study (see appendix, table 1, patients 29, 190 and 205, and the footnote to table 1) a formaldehyde-treated suspension was used. The resultant flocculus was of much finer texture and more easily dispersed. Examined under the dark field microscope, the organisms were seen to be arranged in shreds rather than in clumps. Agglutination occurred at much higher titers with the formaldehyde-treated antigen than with the suspension of living organisms. In testing the human serums in the present series, for which the antigen was used, the flocculus in tubes with a strong reaction was identical microscopically and grossly with that obtained in testing immune rabbit serums with the same type of suspension.

An explanation for this difference in the character of flocculation with the two types of antigen might lie in the possibility that the formaldehyde-treated suspension represents a group-specific antigen, perhaps flagellar in origin and of a protein nature, since it reacts at higher dilutions of serum than does the living suspension. The latter may thus represent a type-specific somatic antigen.

It is possible that there exist several distinct strains of B. bacilliformis, characterized by different serologic specificity. Thus a formaldehyde-treated antigen, representing several of these strains, would be likely to react both with more serums and to a higher titer than an antigen prepared from a suspension of fresh, non-formaldehyde-treated organisms from a single source, i. e., a single strain. The strains included in the antigen which was used were chosen on an empiric basis, as already enumerated, and it was thought, a priori, that by so doing several different antigenic groups might have been included.

All agglutination tests were read after four hours' incubation at 37 C., followed by twelve hours' refrigeration, a hand lens with a power of 10 being used to examine the higher dilutions of serum. Agglutination tests were repeated on all serums after my return to Boston, with freshly prepared antigen identical with that which had been used in Lima. There were no discrepancies of any significance between the two sets of results. Slight agglutination in even

the lowest dilution of serum was considered of diagnostic significance in the light of the general results, and their correlation with the other aspects of the study, in the course of which serum from 35 persons without previous exposure to Carrión's disease failed to show any reaction. Included among these were 13 patients in a large Boston hospital.

RESULTS

Of the whole series of 203 patients, 35.9 per cent showed definite evidence of clinical bartonellosis, either eruption or constitutional symptoms which were accompanied by blood cultures positive for B. bacilliformis. In this percentage were included 5 persons with typical Oroya fever. The serum from 18.7 per cent of the entire series of 203 subjects showed agglutination to varying titer, 3.0 per cent without clinical evidence of disease and 15.8 per cent with evidence of Carrión's disease, either the anemic stage with or without organisms visible in the blood smear or the eruptive stage. In 24.1 per cent of all the patients B. bacilliformis was demonstrated by blood culture, with or without accompanying disease or positive agglutination test. Past history of Carrión's disease was given by 30.6 per cent of all patients, 27.6 per cent without evidence of recurring or persistent disease. These results are summarized in the following tabulation:

Group and Table No.	Blood Cultures *	Agglutination Test	Actual Carrión's Disease: Eruption	Actual Carrión's Disease: Constitutional Symptoms	Past History of Carrión's Disease	Total Number of Patients in Group	Percentage of Series
1	+	+	..	+	—	16	7.9
2	+	+	+	..	—	9	4.4
3	—	+	+	..	—	6	3.0
4	+	—	+	..	—	15	7.4
5	+	—	..	+	—	3	1.4
6	+	5—, 1+	—	—	3+, 3—	6	3.0
7	—	+	—	—	3+, 3—	6	3.0
8	—	—	+	—	—	24	11.8
9	—	—	—	—	+	56	27.6
10	—	—	—	—	—	62	30.5
Number positive...	49	38	54	19	62	203	100.0
Percentage of total...	24.1	18.7	26.6	9.3	30.6		

* Positive or negative for B. bacilliformis.

On the basis of the results of blood cultures and agglutination tests and the presence or absence of clinical disease or past history of it, all of the patients have been divided into ten groups, as indicated in the tabulation. The tables in the appendix at the end of this report show significant details in connection with the patients in each of these categories. In each case the age of the patient, the duration of the total period of residence in endemic regions and the locality or localities where this exposure to infection occurred have been noted. There is also in each case a brief summary of significant points in the history and in the clinical and laboratory observations.

In table 1 are included 16 patients (7.9 per cent of the total number), all of whom had blood cultures positive for B. bacilliformis accompanied by constitutional symptoms to greater or lesser degree. All of the patients in this group showed marked anemia, as indicated by red cell counts or hemoglobin level. In 5 instances this severe anemia was part of the picture of typical Oroya fever in that B. bacil-

liformis was present in abundance in blood films. It is probable that the anemia in a number of other patients in this group might also have been the result of invasion of the blood stream, demonstrated only on blood culture. No organisms were encountered in routine blood smears of these patients, however, since the number of parasitized erythrocytes, if such there were, was too small to be immediately detectable. The patients with Oroya fever (patients 29, 190, 192, 196 and 205) showed a relatively lower titer of agglutinins than many of the other less severely ill persons in this group (patients 12, 141 and 194). Six patients (3, 12, 100, 121, 128 and 131) showed a significant rise in titer or increase in the strength of the agglutination reaction at constant titer on successive occasions during the course of their illness. The importance of this change in the titer is discussed in a later section. Carrión's disease developed in all of the patients in group 1 shortly after exposure in the endemic regions, and hence the periods of incubation had been relatively short.

The patients listed in table 2 (4.4 per cent of the total number) showed the typical clinical picture of verruga peruana, the later eruptive stage of Carrión's disease. The majority showed moderate anemia, less severe than that of the patients in the preceding group and in many instances due probably more to a general stage of malnutrition than to any specific infection. One patient (191) presented a history which in its time sequence is entirely consistent with earlier clinical Oroya fever followed by the typical eruption, here strictly confined in its distribution to areas of skin over joints. The serum from 4 of 9 patients agglutinated to a dilution of 1 : 160. It may be significant that in this group of patients with eruption the titer of agglutinins was higher in a relatively larger number than in the patients in the preceding group, who were in an earlier stage of the disease. The implications of this difference in titer are discussed later.

The patients in table 3 (3 per cent of the total number) differ from those in table 2 only in having blood cultures negative for B. bacilliformis on the single occasion on which they had been bled for serum. One such blood culture obviously did not mean that the blood stream had been consistently sterile. If several blood cultures had been made over a protracted period, it is more than likely that in this group one or more would have been positive for the parasite at one time or another. Four of these 6 patients had a titer of agglutinins of 1:160. It is of interest that 1 of these 4 (patient 204) had lived in endemic regions all of his life and presumably had thus been constantly exposed to infection, yet had no definite past history of any eruption suggesting Carrión's disease.

The patients listed in table 4 (7.4 per cent of the total number) had the typical eruption, and B. bacilliformis was recovered on blood culture. Their serums, however, showed no agglutination. These patients did not differ strikingly, either in duration or extent of disease, from those in table 3, yet agglutinins were not detectable.

The 3 patients in table 5 (1.4 per cent of the total number) had as a definite feature only their blood cultures positive for B. bacilliformis. They also showed symptoms of short duration, which may or may not have had some connection with the infection. It is thus conceivable that these 3 patients should be grouped with those in table 6.

Of the 6 patients in table 6 (3 per cent of the total number), 5 had only a blood culture positive for B. bacilliformis; 3 had a past history of typical eruption as well, and the serum from only 1 patient, who had no actual sign or past history of disease, showed agglutination. The patients in these two groups (tables 5 and 6), representing 4.4 per cent of the total number of persons studied might be called

"carriers." They were virtually asymptomatic, their disease being latent or past, but they still harbored the causative organism in the blood stream.

In table 7 are 6 patients (3 per cent of the total number) for whom a positive agglutination test was the only definite evidence of specific disease. Three had a past history of typical eruption. Again it is possible that had several blood cultures been made in succession over a longer period, they might have been positive for B. bacilliformis on one or more occasions. In this respect these patients are analogous to those in table 3. Two of the 6 patients (65 and 68), being natives of the endemic regions, had had an eruption which may have been that of Carrión's disease and had an agglutination test positive to low titer. Whether this low titer had persisted since the original infection or whether it was the result of inapparent reinfection can only be a matter of speculation. It is possible that a positive agglutination test, in the absence of specific symptomatology, might indicate transient reinfection or a persistent carrier state not detectable by a single blood culture. On this basis, the patients in table 7 would increase the percentage of virtually asymptomatic carriers encountered among the total number of patients seen during the present survey to 7.4.

The majority of patients with clinical disease had both blood cultures negative for the parasite and negative agglutination tests, as shown in table 8 (11.8 per cent of the total number). The data on these patients as to the period of exposure or type and extent of eruption do not differ essentially from the wide variety on patients showing blood cultures positive for the parasite and positive agglutination tests in other groups discussed (tables 2, 3 and 4). The average period of residence in endemic regions, and hence of exposure, of the patients in table 8 is three and five-tenths years. The average for the patients in tables 2, 3 and 4 combined is one and eight-tenths years. The variation among persons is so great, however, that these averages may mean little as a possible basis for explaining the absence of agglutinins in the serum of the group in table 8.

Tables 9 and 10 represent the majority of patients seen. Table 9 (27.6 per cent of the total number) includes all patients with only a past history of Carrión's disease, definitely established in almost every case. It may be of interest that the average duration of residence in endemic regions of the patients in this group is eleven and five-tenths years, far in excess of that of any of the other groups. They thus may represent the most commonly followed pattern in Carrión's disease: clinical disease, in wide variety, followed by lasting immunity against reinfection, without evidence of persistent agglutinins.

In contrast to these patients are those in table 10, representing 30.5 per cent of the total number of patients seen, in whose past history there was nothing to suggest clinically evident Carrión's disease, who showed no evidence of actual infection and whose blood was sterile to culture and did not contain agglutinins for B. bacilliformis. Presumably all of these patients had been more or less constantly exposed to infection, since they were all residents of endemic areas. To be sure, several patients in this group had not been exposed long enough to allow even for minimum incubation periods (i. e., patients 2, 27, 137, 142, 166, 167 and 203), and it is possible that these may later have come down with clinical disease or inapparent infection. It is impossible to say whether some of the patients in this group possessed a natural immunity or one acquired as a result of inapparent infection in the past. It is of interest that natural immunity to the disease seems to be possible even in the presence of inapparent infection (compare the patients in tables 5 and 6).

COMMENT

Clinical Data.—In the whole series there was wide variation in age among patients with different forms of Carrión's disease. It is probable, however, judging from the large number of persons in this series who had had past infection and who had resided in the endemic regions over a long period, that most natives contract the infection in some form in their earlier years, during which their first exposure takes place. The disease, in whatever form it may occur, does not seem to be more severe in one age group than in any other.

The majority of the patients were from the regions represented in the accompanying map, with a few from other endemic areas, such as Yauyos, Canta and Huaráz. There was no predominance of any one type of disease in any one region, since all types of eruption were encountered in both the Rimac and the Santa Eulalia river valley. Puente Carrión, also known as Puente Verrugas, is of historical interest in being one of the most notorious localities for contracting bartonellosis. This bridge is on the railway line from Lima to Oroya which passes through the Rimac river valley. During the construction of the railway 7,000 workmen are said to have perished, most of them of the severe anemic form of the infection, each crosstie on the road costing a human life. This phase of the disease thus came to be known as Oroya fever.[2] Autisha is one of the highest points in the Santa Eulalia valley, where verruga is known to occur in abundance and where many of the patients mentioned here were seen (altitude 2,175 meters above sea level).

In the so-called "classic case" of Oroya fever the incubation period is thought to be ten days to three weeks.[4] The incubation period for the eruptive stage, with or without the anemic stage preceding it, varies much more widely and is not readily delimited. The actual incubation period for a given patient in the present series was difficult, if not impossible, to determine, since among the patients seen the duration of residence in the endemic regions, and hence of exposure, varied so greatly. There were many patients who had had but a few weeks to a few months of exposure in whom the severe form of the disease developed. On the other hand, there was 1 patient (table 1, patient 29) who had lived in the endemic region of the Santa Eulalia valley for eight years without sign or symptom before contracting severe Oroya fever. What factors determine the incubation period are not known. It is obvious that the duration of exposure bears no direct relation to the type or the severity of the ensuing disease.

The usual course of events is for one attack of Oroya fever or of verruga in any form to confer lasting immunity. Recurrence of Oroya fever is rare and was not encountered during the course of the present study. The recurrence of the typical eruption, however, is not uncommon. There were 4 patients with such recurrences in the present series (table 9, patients 48, 78, 84 and 106), 1 of them (patient 106) claiming to have had five attacks in all of typical verruga peruana. Whether these recurrent attacks represented acute exacerbations of persistent inapparent infections or actual reinfections is not clear.

Of great interest also were those persons with actual inapparent infection who harbored the organism, as shown by blood culture, but who were entirely asymptomatic or had only mild nonspecific complaints. A few had a past history of verruga, some with and some without a positive agglutination test. Such persons, along with patients with frank Oroya fever and verruga, may represent a natural reservoir of infection and serve as carriers to maintain the infection in wild sandflies in a given locality or to carry infection from one site to another.

4. Rebagliati, R.: Verruga peruana, Lima, Imprenta Torres Aguirre, 1940.

The symptoms which accompanied either form of the disease were variable when present. In the anemic patients, who also had usually moderate to marked elevation of temperature, there were symptoms characteristic of any anemia or fever, such as extreme fatigue, general prostration, dizziness, anorexia and thirst. Late in the anemic stage or early in the eruptive stage many patients complained of pain in the long bones and of severe arthralgia. The eruption, in many instances, was situated over bony prominences or over joints. One patient (table 2, patient 191), who presented a story entirely consistent with severe Oroya fever preceding his eruption, had nodules strictly confined to areas of skin directly over joints, large and small, of all four extremities. In other instances of extensive eruption the nodules were distributed at random, usually over the extremities and the face, and the miliary form on the trunk only. In the case of miliary nodules the eruption was often generalized.

Blood Cultures.—The morphology of the various strains mentioned in the tables refers to observations made on second and third transfers from original blood cultures. It will be seen that there is a wide variety of growth characteristics, from large coarse granular colonies scattered at random throughout the medium to a fine cloudy type of growth confined to a sharp level usually in the upper 2 cc. of medium. Often there were large granular colonies surrounded by a halo of satellite colonies. All of these strains were examined with the dark field microscope for the presence of motile organisms and spirals. It has been thought probable [5] that the presence and quantity of the fine rigid spirals often seen in the dark field microscope in large numbers loosely attached to colonies of organisms are an index of earlier motility of the strain in question. Actual motility is more easily demonstrated in young cultures on Geiman blood agar, to which a number of the new strains enumerated here have been transferred for further study. It will be seen that there is no correlation of the type of growth or the presence of spirals to the type, severity or duration of the clinical disease in a given case.

Studies of the Blood.—In those patients with frank Oroya fever the degree of anemia was remarkably severe, in 3 cases (patients 29, 190 and 205) the erythrocyte count falling below 1,000,000 cells per cubic millimeter and the hemoglobin reaching extremely low levels. There was also severe anemia in the other patients with invasion of the blood stream demonstrated by blood cultures only and with marked constitutional symptoms (table 1). The type of anemia in these patients was usually normocytic or slightly macrocytic and hypochromic as judged by examination of a blood smear. It is difficult to explain the rather marked anemia encountered in some of the patients with eruption purely on the basis of persistent invasion of the blood stream by B. bacilliformis. Often, in addition, there was profuse bleeding from ulcerated and ruptured nodules, leading to marked secondary anemia. Malnutrition among the native population is prevalent to a degree so distressing that various deficiencies must be considered as playing a highly important part in the blood picture of all of the patients seen. Widespread occurence of intestinal parasitic diseases, as well as malaria and tuberculosis, must also be counted among the many factors in this moderate to severe anemia encountered in the native population. It is of interest that marked leukocytosis was the exception in the present series and occurred in severe cases of Oroya fever usually only where there was definite evidence of serious secondary infection (table 1, patient 196).

Agglutinins.—Among the chief objectives of the present study were the following ones to determine (*a*) at what stage during the course of natural infection

5. Geiman, Q. M.: Personal communication to the author

with B. bacilliformis there might be a rise in specific humoral antibodies detectable by means of the agglutination test, (*b*) how long these agglutinins persist after the peak of the infection and (*c*) whether agglutinins play any part in immunity.

In an attempt to determine at what stage of the disease agglutinins appear, all of those patients showing definite eruption or constitutional symptoms referable to blood cultures positive for B. bacilliformis with or without titer of agglutinins have been represented in the accompanying chart (fig. 3), the titer of agglutinins where they occurred being plotted against the duration of the disease. Those patients not showing a titer of agglutinins are indicated in the separate strip underneath the main body of the chart. Each vertical line represents a single patient. The blood cultures made at the same time as the serologic tests are indicated as positive or negative, and each patient's illness is designated as eruptive, severely anemic (Oroya fever) or accompanied by constitutional symptoms. In only a few instances was more than one agglutination test on one occasion done during the course of a given patient's illness.

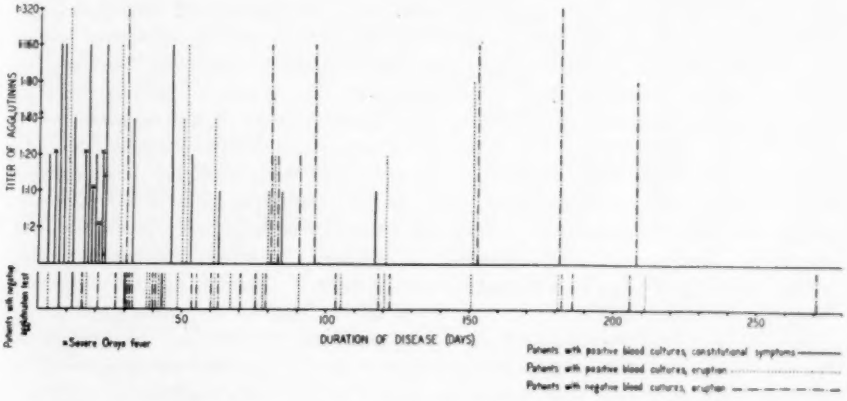

Fig. 2.—The relation of agglutinins for B. bacilliformis to clinically evident Carrión's disease.

Seventy-three patients are represented in the chart. Of these, 32.9 per cent had typical verrucous eruptions, early or late, with blood culture negative for B. bacilliformis and negative agglutination test; 21.9 per cent had constitutional symptoms, chiefly those due to severe anemia (including 5 instances of proved Oroya fever, blood cultures positive for the parasite and positive agglutination test to varying titer); 20.5 per cent had positive cultures and negative agglutination tests but typical eruption; 12.3 per cent had positive cultures and agglutination tests and typical verruga; 8.2 per cent had typical verruga and negative agglutination tests and blood cultures, and 4.2 per cent had positive blood cultures, negative agglutination tests and constitutional symptoms probably due to proved infection.

It is obvious that no 2 cases would be exactly similar with respect to incubation period, duration of acute anemic stage or eruption. Rather the reverse was true in that there was wide variation in these factors, as far as they could be determined. They cannot therefore be exactly superimposed to give an accurate composite picture of the course of the disease as a whole. But it does appear likely, from the evidence as graphically outlined, that the majority of patients showed a

significant titer of agglutinins, often as high as 1 : 320, in the earlier stages of the disease. In other words, those patients who were tested during the anemic stage or during the first part of the eruptive stage were more likely to show significant titer than those patients who had recovered completely or who had had a minimal or extensive eruption over a relatively longer period. Of those patients in the earlier stage of the disease, either anemic or eruptive, showing moderate or high titer of agglutinins, by far the majority also had blood cultures positive for B. bacilliformis. The majority of these were either patients with severe anemia with organisms visible in the blood film or patients with severe constitutional symptoms explainable only on the basis of infection with B. bacilliformis, proved by blood culture. Of those patients showing a definite titer of agglutinins much later in the course of their disease, the larger part had blood cultures negative for the parasite and were in the eruptive stage. Though there are a few discrepancies between these two general categories, i. e., those early in the acute stage of the disease with positive blood cultures and positive agglutination test and those later in the course with eruption, negative blood cultures and positive agglutination tests, it appears likely that agglutinins, when they do appear, are detectable early in the acute stage of the disease, while blood cultures are still positive. They may persist into the eruptive stage after blood cultures have become negative. It should not be inferred, however, that blood cultures invariably become negative when the eruptive stage has developed, since in many cases organisms were recovered from the blood stream even after the eruption had completely subsided. The probability that agglutinins usually do not persist after the complete disappearance of the eruption is substantiated by data on the patients in table 9, all of whom had a past history of eruption or proved infection, with an average of five and nine-tenths years since the termination of disease. The only exception to this picture are 3 of the 6 patients represented in table 7 (patients 65, 68 and 162). These persons had past histories suggestive of verruga, as well as agglutinins to varying titer. For these patients it is impossible to tell whether the agglutinins had persisted since the original clinical disease or had reappeared as a result of more recent inapparent infection.

It is possible that in some of the infections of longer standing (table 7, patients 35, 39, 145 and 185) there might have been agglutinins earlier in the course of the disease. This is only speculation, however, and the only other conclusion to be drawn in the light of the evidence at hand is that in not all cases of even the most typical eruption is a measurable titer of agglutinins produced.

Conversely, it is unlikely that agglutinins play any significant part in the lasting acquired immunity which almost invariably follows the typical clinical disease. This is again evident from the patients listed in table 9. These all had had typical Carrión's disease in varying degree, which was apparently followed by lasting immunity, since in most cases there was no definite recurrence of eruption in spite of prolonged exposure by virtue of residence in endemic regions subsequent to the actual clinical disease. Recurrence of frank Oroya fever, as has been stated, is rare and was not encountered in the present study.

The question of the mechanism of immunity has been approached from another angle, that of active and passive immunization. Three patients with severe Oroya fever (table 1, patients 29, 190 and 205) were treated with a large quantity of hyperimmune rabbit serum of high agglutinin titer, prepared by repeated intra-

venous injection into rabbits of living B. bacilliformis.[6] The fact that these three attempts at passive immunization did not clear the blood stream of organisms is some indication that immunity to B. bacilliformis is not of the rapidly sterilizing type.

This possibility is also suggested by the preliminary results of another experiment[7] still in progress involving active immunization of persons without previous exposure to infection by Bartonella. Twenty-two members of a military detachment, assigned to guard duty at three heavily infected localities in the Rimac river valley, were each given subcutaneously 1 cc. of a formaldehyde-treated suspension of B. bacilliformis (identical with that used in performing routine agglutination tests) before taking up their posts. They were given 1 cc. more after one week's tour of duty. Three weeks to one month after the first injection all showed agglutinins for B. bacilliformis. There was no agglutination in any case or in any dilution with serum taken before immunization. At the end of about five months of continuous residence in the endemic regions, none of the men showed any signs of severe illness, but from 11 of them B. bacilliformis was recovered by blood culture. The blood in every case before immunization and exposure had been sterile to culture. It seems evident, therefore, that the production of specific agglutinins in human beings by inoculation with a formaldehyde-treated suspension of B. bacilliformis does not in all cases prevent infection. It appears possible, however, that such immunization might ameliorate the course of potential Carrión's disease in persons not previously exposed, since none of the group in question was incapacitated as a direct result of proved infection. No final conclusions concerning the efficacy of active immunization in the prevention of Carrión's disease can of course be drawn until the data from these preliminary experiments on vaccination are completed and further application in the field is carried out.

SUMMARY

A total of 203 inhabitants of two valleys on the Pacific slope of the Peruvian Andes in the foothills near Lima and natives of other parts who had come to Lima for hospitalization were examined for actual evidence or past history of Carrión's disease. All were or had at one time been residents of regions where bartonellosis is endemic. Blood cultures on special Bartonella medium were made for each person. An agglutination test, using formaldehyde-treated suspensions of B. bacilliformis, was performed on serum from each patient, once in Lima and again in Boston with freshly prepared antigen. Routine studies of the blood were performed when indicated, with special emphasis on the possibility of encountering the specific organism in blood smears stained with Giemsa's stain.

Important clinical data, including age incidence, geographic distribution, variety of symptomatology and types of disease encountered, are discussed in relation to pertinent laboratory studies. Special emphasis is placed on the discussion of agglutinins and their role in acquired, active and passive immunity to infection with B. bacilliformis.

6. Data on these 3 patients are to be reported in detail at a later date (Arch. Int. Med., to be published).

7. The experiment is being conducted in collaboration with Dr. Marshall Hertig, of the National Institute of Hygiene and Public Health, Lima, and is to be reported in detail at a later date. Dr. Q. M. Geiman, of the Department of Comparative Pathology and Tropical Medicine, Harvard Medical School, prepared and sent to Lima at short notice a portion of the vaccine used on some of the patients in this immunization experiment.

TABLE 1.—*Patients With Blood Culture Positive for B. Bacilliformis, Positive Agglutination Test and No Eruption or Past History of Carrión's Disease, but With Constitutional Symptoms*

Patient No.	Age, Yr.	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Agglutination Test 1 2 3 4 5 6	Studies of the Blood	Comment
3	32	3 mo.; Puente Carrión	Pains in bones; headache; febrile symptoms for 5 wk., beginning 1 wk. before end of period of exposure	A and B: positive, varied granular growth; DF, no spirals	A: 2 1 0 0 B: 4 4 3	A: R. B. C. 2,530,000, hb. 7.4 Gm.; B: R. B. C. 3,540,000, hb. 9 Gm.	Laboratory data: A at beginning of symptoms, B 1 mo. later; no eruption or marked fever
12	51	6 mo.; Yauyos	Fatigue, "fever" and lethargy for 1 mo., climaxing about 2 yr. of general ill health and vague complaints not accurately recalled	A and B: positive; large, granular colonies; sharp level	A: 2 2 2 2 2 1 B: 4 4 4 3 3 2	A: R. B. C. 1,580,000, hb. 8.25 Gm.; hematocrit reading 1.8; B: R. B. C. 2,450,000, hb. 5 Gm.; no bartonellas in blood film	Seen in hospital; history of untreated chancre, Wassermann reaction +, Kahn reaction 4+; laboratory data: A 23 days and B 45 days after onset of acute symptoms; 3 typical verrucous nodules developed 53 days after onset; death from generalized tuberculosis about 3 mo. after onset of acute symptoms
100	19	9 mo.; Huinco	Pains in bones, occasional chills and fever for 2 mo.	A and B: positive; granular growth; DF, no spirals	A: 0 0 0 B: 2 1 0	A: R. B. C. 2,360,000; hb. 7.25 Gm.	First seen in field, later at hospital after admission with temperature of 103 F.; laboratory data: A in field, B 1 mo. later on admission to hospital; no eruption
111	24	2 mo.; Puente Carrión	Temperature 101.8 F.; pulse 120; general malaise, anorexia, pains in bones, loss of weight for 47 days preceded by 5 days of chills, fever and night sweats	Positive; DF, no spirals	2 2 1 0	R. B. C. 2,850,000; hb. 5.5 Gm.	Extreme conjunctival pallor; no jaundice; sent to hospital 2 days after present data taken; no follow-up
121	25	41 days; Puente Carrión	Malaise, "fever," night sweats and arthralgia for 2 mo.	Positive; varied granular growth; sharp level; DF spirals	A: 2 1 0 0 0 B: 2 1 1 0	A: hb. 10.5 Gm.; B: hb. 10.25 Gm.	Laboratory data: A after 2 mo. of symptoms, B 2 wk. later than A, symptoms having continued
128	29	3 yr. (1928-1931), Huinco; 2 mo. in 1933, Canta; 124 days prior to date of present data at Puente Challape	Well up to 117th day of most recent period of exposure, when articular pains, malaise and nocturnal fever started	A: positive, cloudy growth, DF spirals; B: negative; C: positive	A: 0 0 0 B: 3 3 2	A: hb. 9.5 Gm.; B: R. B. C. 4,000,000, hb. 9 Gm.	Laboratory data: A 105th day of most recent period of exposure, B 19 days later on 124th day of same period, C 70 days after end of period
131	24	110 days; Puente Challape	Occasional chills and fever throughout period of exposure; temperature 99.4 F. on 11th day and 100 F. on 21st day after end of period of exposure	A: cultures contaminated; B: positive, granular sharp level, DF spirals	A: 0 0 0 B: 2 1 0 C: 3 2 1	A: hb. 9.4 Gm.; B: hb. 9.0 Gm.	Laboratory data: A 105th day of period of exposure, B 11 days and C 21 days after end of period
141	26	119 days; Puente Carrión	Arthralgia and pains in bones during last 3 wk. of period of exposure	A: positive, large granular colonies, sharp level, DF, no spirals	A: 3 3 3 2 2 1 B: 3 3 3 3 3 2	A: hb. 9.25 Gm.; B: R. B. C. 3,900,000; hematocrit reading 16	Laboratory data: A 114th day of period of exposure, B 8th day after end of period; 1 subcutaneous nodule on each knee 16 days after end of period

194	25	20 days about 1 mo. prior to date of present data	Headache, malaise, febrile symptoms, pains in bones and anorexia for 1 wk.	Positive; DF, many spirals	4 3 3 3 2 1	R. B. C. 1,750,000; W. B. C. 8,200; hb. 4.75 Gm.; hematocrit reading 26	Seen in hospital; treated with intravenous administration of glycerin; no follow-up
200	24	92 days; Puente Carrión	Chill and fever on 84th day of period of exposure; anorexia and jaundice for 2 days	Positive; heavy granular level; DF, no spirals	3 2 1 1 0 0	R. B. C. 3,590,000; W. B. C. 8,100; hb. 7.8 Gm.	Seen in hospital; general symptoms improved; no follow-up
70	41	26 mo.; Callahuanca, Autisha	Three days of chills	Positive; large colonies, wide halos, DF spirals	3 2 1 0 0 0	Hb. 9.75 Gm.	Symptoms only suggestive of Carrión's disease
192	30	July 1941 8 days, Dec. 1941 2 wk., Feb. 1942 2 wk.; Huaráz	15 days of fever, beginning with 1 chill; loss of weight; moderate icterus	A: positive; B: positive, cloudy level; C; positive, finely cloudy and granular growth; DF spirals	A: 2 1 1	A. R. B. C. 2,050,000, hb. 7.5 Gm., B. bacilliformis in 28% of R. B. C.; B: R. B. C. 2,070,000, hb. 7.1 Gm.*; C: R. B. C. 2,500,000, hb. 7.75 Gm.*; B. bacilliformis in 70% of R. B. C.	Seen in hospital; typical Oroya fever; laboratory data: A 15th day, B 18th day and C 19th day of illness; from 14th to 25th day transfusion of 2,250 cc. whole normal blood and 500 cc. blood from person recovered from verruga; subsequent eruption and recovery with negative blood cultures 5 mo. after onset
196	21	1 mo.; Autisha	Vague illness lasting 3 wk.	Positive; granular and cloudy level; DF spirals	2 0 0 0 0 0	R. B. C. 1,740,000; W. B. C. 16,600; hb. 4 Gm.; B. bacilliformis in 78% of R. B. C.	Seen in hospital; typical Oroya fever; died in 6th week of illness; autopsy: severe colitis of undetermined origin
29	51	8 yr.; Callahuanca, Barbablanca, Autisha	Sudden chills, fever and malaise for 18 days; jaundice for 2 days	A: negative; B: positive; finely granular growth, DF spirals; D: negative	A: 0 0 0 0 0 0 B: 4 1 0 0 0 0	A: hb. 11 Gm.; B: R. B. C. 4,600,000, W. B. C. 7,000, no organisms in smear; C: R. B. C. 1,430,000, W. B. C. 9,300, hb. 5 Gm.*, hematocrit reading 20, B. bacilliformis in 25% of R. B. C.	Seen in hospital; typical Oroya fever; laboratory data: A 15 days before, B 13 days after, C 18 days after and D 2 mo. after onset of illness; treated with 50 cc. anti-Bartonella-bacilliformis rabbit serum; recovery in 2 mo.; no eruption
190	15	8 days ending 1 mo. prior to present data; Rimac river valley, Matucana	Onset of fever, headache, malaise and jaundice 15 days after end of period of exposure	Positive; finely granular growth	4 4 1 0 0 0	R. B. C. 610,000; W. B. C. 14,000; hb. 3 Gm.*; hematocrit reading 8; B. bacilliformis in 86% of R. B. C.	Seen in hospital; typical Oroya fever; treated with 60 cc. anti-Bartonella-bacilliformis rabbit serum; miliary eruption on 29th day of illness; complete recovery
205	21	6 mo. ending 34 days prior to present data; Chinchipe	Onset of chill, headache, malaise, vomiting of coffee-colored material and jaundice 13 days after exposure	Positive; finely granular growth; DF, no spirals	3 1 1 0 0 0	R. B. C. 880,000; W. B. C. 13,200; hb. 3.25 Gm.*; hematocrit reading 10; B. bacilliformis in 63% of R. B. C.	Seen in hospital; typical Oroya fever; treated with 50 cc. anti-Bartonella-bacilliformis rabbit serum; eventual recovery, with appearance of eruption 3 mo. after onset of illness

A statistical analysis of the types of disease encountered, with relevant clinical and laboratory observations, is included in ten tables in an appendix at the end of this report. These serve to emphasize the wide variety of clinical and laboratory data encountered in a significantly large series of cases.

CONCLUSIONS

From an analysis of the results of agglutination tests and blood cultures and the course of disease in each patient it becomes evident that a measurable titer of agglutinins is probably not produced in all persons with Carrión's disease. On the other hand, it appears that agglutinins, when they do occur, are detectable most often during the early acute anemic stage of the disease (clinical or subclinical Oroya fever), when blood cultures are regularly positive for B. bacilliformis and the parasite is often detectable in the blood smear. It may not be premature to conjecture that the titer of agglutinins encountered at this stage is proportional to the severity of the preeruptive invasion of the blood stream, and to the patient's response to such invasion as evidenced by the severity of symptoms and other relevant clinical data.

From observations made on several patients at different stages of their disease it is probable that the titer of agglutinins rises and most often reaches a peak just prior to the appearance of the eruption. As observed in the majority of cases in which eruption occurs, there is apparently a decline in titer as the eruption progresses and finally subsides. In the majority of cases after all evidence of eruption has subsided, no agglutinins are found in the serum. In many instances, blood cultures positive for B. bacilliformis may outlast the duration of the agglutinin response. Rarely is the reverse the case.

It appears unlikely that agglutinins play any major part in the almost universal acquired immunity which follows the typical clinical disease or in the apparent immunity which may be present in long term residents of endemic areas, who deny a past history of Carrión's disease.

Conversely, it appears improbable that the production of agglutinins for B. bacilliformis in nonimmune persons by actitve immunization with formaldehyde-treated vaccine prevents asymptomatic infection of the blood stream. Likewise, it is evident that administration of specific hyperimmune rabbit serum of high agglutinin titer does not sterilize the blood stream completely in cases of severe Oroya fever.

The agglutination test made with a formaldehyde-treated suspension of B. bacilliformis may be of some aid in the diagnosis of unexplained fever, anemia and constitutional symptoms, representing mild or severe illness preceding a later recognizable eruption in a person who is likely to have been exposed to infection. The agglutination test would not, however, seem to be of great use either in determining past infection or in estimating the degree of immunity in persons who claim to have had Carrión's disease.

Agglutination in even the lowest dilutions of serum is thought to be of diagnostic significance.

APPENDIX

On the basis of results of blood cultures and agglutination tests and of the presence or absence of clinical disease or past history of it all of the patients studied have been divided into ten groups (see the tabulation in the text, paragraph 1 under "Results"). The data on all of the patients involved in the present study are compiled in the ten corresponding tables which follow.

TABLE 2.—*Patients With Blood Culture Positive for B. Bacilliformis and Positive Agglutination Test, in Eruptive Stage of Carrión's Disease With or Without Constitutional Symptoms, But With No Past History of the Disease*

Patient No.	Age, Yr.	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Agglutination Test 1 2 3 4 5 6	Studies of the Blood	Comment
5	50	8 mo.; Autisha	Extensive eruption; large verrucomas present on arms, legs and face for 4 mo.	Positive; granular growth	3 2 1 0	R. B. C. 2,440,000; W. B. C. 6,800; hb. 7.5 Gm.	Extensive hemorrhage from nodules; eruption still present 1 mo. later
37	28	7 mo.; Autisha	Scattered subcutaneous nodules and pains in bones present for 3 mo.	Positive; cloudy, sharp level; DF, spirals	2 1 0	Hb. 10 Gm.	
51	9	12 mo.; Huinco	Generalized miliary eruption for 3 mo.	Positive; granular and cloudy level; DF, no spirals	3 3 2 0	R. B. C. 3,000,000; hb. 8.25 Gm.	Eruption still present 5 mo. after onset
177	23	10 mo.; Puente Carrión	Fever, malaise, diarrhea and headache for 47 days; 1 cm. nodule on right thigh for 1 wk.	Positive; granular and cloudy sharp level	3 2 1 1 1 1	R. B. C. 1,240,000; hb. 3.75 Gm.; hematocrit reading 14; no Bartonella in blood film	Seen in hospital; severe amebiasis; continued anemia; fever; no follow-up
181	25	1 mo.; Yauyos	Moderate sudaminous eruption for 3 wk.; 1 subcutaneous nodule for 1 wk.	Positive; scattered granular colonies; DF, spirals	4 3 3 2 1 1	R. B. C. 1,240,000; W. B. C. 8,500; hb. 5.5 Gm.; hematocrit reading 16	Seen in hospital; moderately febrile course; no follow-up
183	14	2 mo. ending 5 mo. prior to date of present data; Loya valley	Extensive confluent eruption on both lower legs, less on arms, for 1½ mo.; preceded by fever and minimal pains in bones at sites of eruption for 1 wk.	Positive; fine granular growth; DF, spirals	3 1 1	R. B. C. 3,470,000; W. B. C. 7,200; hb. 8.25 Gm.; hematocrit reading 36	Seen in hospital; afebrile course
188	37	4 mo.; Huaráz	One medium-sized nodule for 2 mo.; preceded by severe constitutional symptoms	Positive; fine granular growth; DF, no spirals	4 3 2 1 0 0	R. B. C. 4,330,000; hb. 6.5 Gm.; hematocrit reading 25	Seen in hospital
189	22	3 mo.; Callahuanca	One verruga, 1 subcutaneous nodule for 10 days; preceded by vague general complaints	Positive; granular and cloudy growth; DF motility	2 2 1 1 1 1	No Bartonella in blood film	Seen in hospital; Kahn reaction 3+; Wassermann reaction —
191	14	2 yr.; Yauyos	Extensive nodular eruption over all joints of extremities for 2 mo., preceded by constitutional symptoms, jaundice and pains in bones for 3 mo.	Positive (subcultures contaminated)	2 1 1 1 1 0	R. B. C. 4,000,000; hb. 7.5 Gm.; hematocrit reading 28	Seen in hospital; story consistent with Oroya fever followed by typical eruption; fever during 1st 3 days of eruption

TABLE 3.—*Patients With Blood Culture Negative for B. Bacilliformis and Positive Agglutination Test, in the Eruptive Stage of Carrión's Disease With or Without Constitutional Symptoms, But With No Past History of the Disease*

Patient No.; Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Agglutination Test 1 2 3 4 5 6	Studies of the Blood	Comment
14 22 yr.	1 yr.; Autisha, Huinco	Eruption for 3 mo. preceded by fever and pains in bones for 3 days; subcutaneous nodules on left ankle and forearm	3 2 1 0	R. B. C. 4,360,000; W. B. C. 6,600; hb. 12.25 Gm.	
122 32 yr.	1 mo. a year prior to present data, Chaupichaca; 10 days prior to present data, Puente Carrión	Subsiding minimal miliary eruption present for 7 mo.; preceded by febrile symptoms for 4 mo.	A: 0 0 0 B: 0 0 0 C: 2 3 3 2 —	B: hb. 11 Gm.	Hands, arms and neck covered with sandfly bites; laboratory data: A after 10 days, B after 25 days and C after 36 days at Puente Carrión; no change in clinical course
174 3 yr.	Life; Pallie	Eruption present for 6 mo.; 1 cm. nodules on legs and arms; preceded by febrile symptoms for 2 mo.	3 2 2 1 1 1	R. B. C. 2,390,000; hb. 4.5 Gm. hematocrit reading 16	Conjunctivas extremely pale
180 46 yr.	4 mo.; Huinco	Generalized miliary and nodular eruption present for 1 mo.; preceded by generalized pains in bones and irregular fever for 2 mo.	4 4 3 3 2 2	R. B. C. 2,620,000; W. B. C. 6,400; hb. 7.75 Gm.; hematocrit reading 21	Seen in hospital; admitted 1 mo. prior to date of present data; slight fever during 1st few days, no fever thereafter
184 26 yr.	9 mo. ending 5 mo. before date of present data; Yauyos	Eruption present for 5 mo., having appeared during last month of period of exposure; 1 large nodule on right arm; subcutaneous nodules on the shins	4 4 4 2 1 1	R. B. C. 3,510,000; W. B. C. 6,600; hb. 8 Gm.; hematocrit reading 30	Seen in hospital; moderately febrile course, with temperatures, not above 39 C. (102.2 F.); Kahn reaction 2+; Wassermann reaction —
204 22 yr.	Whole life save 6 mo. ending 10 mo. before date of present data, return to endemic region for 6 mo. ending 3 mo. before present data; Yauyos	1 nodule on right elbow, present for 16 mo.; malaise, anorexia, pains in bones and night sweats present for 2 mo.	3 4 4 4 3 1	R. B. C. 2,000,000; hb. 6.25 Gm.	Seen in hospital

All periods appearing in any column in the tables are represented as ending on the date on which the data and blood for the present investigation were taken, unless otherwise specified in individual cases. Original blood cultures are labeled either positive or negative, according to whether typical growth of B. bacilliformis was detected grossly and confirmed by dark field examination after the proper incubation. The morphologic details mentioned refer to observations made on second and on third transfer from original blood cultures. All of these transfers were examined with the dark field microscope (indicated by "DF") and indication is given in each case where spirals or actual motile organisms were encountered. As mentioned in the text of this report, these spirals are thought to be an index of earlier motility of a given strain. The numbers 1 through 6 at the head of the column giving the results of the agglutination tests represent, respectively, final dilutions of serum, after addition of the antigen, of 1:2, 1:10, 1:20, 1:40, 1:80 and 1:160. The strength of the reaction in each case is graded from 4 to 0, 4 indicating a heavy flocculus with clear supernatant fluid, 3 to 1 indicating that agglutination was progressively less marked and 0 indicating that no agglutination occurred. A dash (–) indicates that no test was performed for a given dilution. Values for hemoglobin are expressed as grams per hundred cubic centimeters, and an asterisk indicates that a value determined by the method of Sahli was checked by means of an electric photocolorimeter.

TABLE 4.—*Patients With Blood Culture Positive for B. Bacilliformis and Negative Agglutination Test, in Eruptive Stage of Carrión's Disease With or Without Constitutional Symptoms, But With No Past History of the Disease*

Patient No.; Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Studies of the Blood	Comment
8 21 yr.	7 mo.; Autisha	Pain in bones for 4 mo.; eruption for 2 mo. with small nodules on lower legs and 1 or 2 at each elbow	Positive; varied granular and cloudy level; DF, spirals	R. B. C. 3,960,000; hb. 10 Gm.; hematocrit reading 33	
10 27 yr.	4 mo.; Autisha	Recent eruption, still present; 4 large subcutaneous nodules	Positive; granular growth, no level; DF, spirals	R. B. C. 3,290,000; hb. 8.75 Gm.	
19 27 yr.	1 yr.; Autisha	Eruption for 40 days with 2 nodules and 2 subcutaneous lesions; preceded by 1 wk. of febrile symptoms	Positive; finely cloudy, sharp level; DF, spirals	R. B. C. 4,670,000; hb. 11.5 Gm.	Eruption present 2 mo. after present data taken
36 21 yr.	9 mo.; Huinco, Autisha	3 moderately large subcutaneous nodules and smaller scattered nodules present for 1 mo.; preceded by 1 wk. of febrile symptoms and pains in bones	Positive; cloudy level; DF, spirals	R. B. C. 3,970,000; hb. 9 Gm.	
45 30 yr.	6 mo.; Autisha	1 mo. of slight malaise; small incipient subcutaneous nodules for 6 days	Positive; varied granular and cloudy, sharp level; DF, spirals	Hb. 8.25 Gm.	
54 19 yr.	11 mo.; Huinco, Autisha	Pains in bones for 1 mo. and 1 subcutaneous nodule which subsided 7 mo. prior to present data; general symptoms persisted	Positive; cloudy sharp level; DF, spirals	Hb. 10.25 Gm.	Infection probably extended over 7 mo.
61 23 yr.	7 mo.; Huinco	2 wk. of miliary eruption on both lower legs and forearms; 2 days of fever 2 wk. prior to eruption	Positive; fine irregular, bunchy growth, no level; DF, no spirals	Hb. 9.75 Gm.	
73 2 yr.	7 mo.; Autisha	Eruption present for 2 mo.; preceded by 1 wk. of fever, anorexia and sweating; many small nodules, widely scattered	Positive; cloudy and granular growth; DF, spirals	R. B. C. 3,970,000; hb. 9 Gm.	
74 23 yr.	7 mo.; Autisha	Eruption present for 3 mo.; 2 subcutaneous nodules on left elbow	Positive; finely granular, sharp level; DF, spirals	Hb. 9.25 Gm.	
80 44 yr.	1 yr.; Autisha	Pains in bones of leg for 35 days, followed by minimal miliary eruption on both wrists	A, B: positive; varied granular growth; DF, spirals	A: hb. 10.75 Gm.; B: hb. 10.5 Gm.	Laboratory data: A after 1 mo. of symptoms, B 11 days later, 1 wk. after eruption appeared
101 29 yr.	1 yr.; Barbablanca	1 subcutaneous nodule for 1 mo., preceded by 8 days of febrile symptoms	Positive; large and small colonies, with large halos; DF, spirals	Hb. 9 Gm.	Profuse bleeding from nodule
168 18 yr.	8 yr.; Santa Eulalia	Minimal miliary eruption present on lower legs and forearms for 3 mo.; preceded by febrile symptoms for 2 mo.	Positive; varied granular and cloudy growth; DF, spirals		
182 30 yr.	6 mo.; Yauyos	Eruption present for 60 days; nodule on right knee and arm; legs covered with brawny vestiges of verrucous eruption, which had been preceded by vague febrile symptoms for 1½ mo.	Positive; varied granular sharp level; DF, spirals	R. B. C. 3,160,000; W. B. C. 8,900; hb. 8.25 Gm.	Seen in hospital; schizonts and gametes of Plasmodium vivax in blood film; chart unremarkable
197 19 yr.	5 mo.; Yauyos	Eruption present for 3 mo.; subcutaneous nodules on lower extremities, preceded 4 mo. earlier by irregular fever, ? jaundice, anorexia and splenomegaly	Positive; sparse finely granular colonies; DF, no spirals	Hb. 10 Gm.	Seen in hospital; spleen palpable, hard, painful
15 25 yr.	4 mo.; Huinco, Autisha	2 to 3 subcutaneous nodules on arms and legs present for 2 mo., preceded by pains in the bones and night sweats for 2 mo.	Positive; roughly granular growth; DF, spirals	R. B. C. 4,000,000; W. B. C. 4,800; hb. 12.0 Gm.	In Huinco at time eruption appeared

TABLE 5.—*Patients With Blood Culture Positive for B. Bacilliformis and Negative Agglutination Test, With No Eruption or Past History of Carrión's Disease, But With Constitutional Symptoms*

Patient No.; Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Studies of the Blood	Comment
77 29 yr.	1 yr.; Autisha, Huinco	1 wk. of pains in bones of extremities and general malaise	Positive; finely granular growth, sharp level	Hb. 9.75 Gm.	
136 24 yr.	110 days; Puente Challape	Headache and pains in bones for 3 to 4 days after end of period of exposure	A: contaminated; B: positive, DF spirals	A: hb. 9.25 Gm.; B: hb. 9.25 Gm.	Laboratory data: A 105th day of period of exposure and B 11 days after end of period
179 45 yr.	20 days at Huinco, ending 45 days before date of present data	Fever; generalized aches and pains, marked in legs, night sweats, weakness, diarrhea and epigastric pain for 1 mo.	Positive; cloudy growth, indefinite level; DF, spirals	R. B. C. 1,340,000; W. B. C. 6,100; hb. 4.75 Gm.; hematocrit reading 14	Seen in hospital; irregular moderately febrile course, with temperature not over 38.4 C. (101.1 F.); severe anemia; B. bacilliformis reported in smear earlier in course of illness, with erythroblasts and normoblasts

TABLE 6.—*Patients With Blood Culture Positive for B. Bacilliformis, Without Symptoms and With or Without a Past History of Carrión's Disease*

Patient No.; Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Blood Cultures	Agglutination 1 2 3 4 5 6	Studies of the Blood	Comment
138 26 yr.	110 days Puente Quita Sombrero, Puente Carrión	? Pains in bones 1 mo. after end of period of exposure	A: positive, sharp irregular level, DF, spirals; B: positive	A: 0 0 0	A: hb. 10.5 Gm.	Laboratory data: A 105th day of period of exposure, B 1 mo. after end of period
66 21 yr.	Native of Yauyos; 3 yr. in Huinco	No past history or actual symptoms of verruga	Positive; granular and cloudy level; DF, spirals	0 0 0	Hb. 10.5 Gm.	Reported as still asymptomatic 2 mo. after present data taken
195 36 yr.	1 mo. at Puente Carrión 1½ yr. prior to present data; at Puente Challape for brief period just prior to present data	Miliary eruption on arms, legs and face for 1 yr. ending 6 mo. prior to present data; occasional pains in bones, chills and fever to present time	Positive; 2 cloudy levels, occasional large colony; DF, spirals	0 0 0	R. B. C. 3,570,000; hb. 9 Gm.	
7 36 yr.	3 yr. at Barbablanca; 10 mo. at Autisha	Eruption for 8 mo. 5 yr. prior to present data; 1 subcutaneous nodule on lower leg with minimal miliary eruption; no signs or symptoms at time of taking data	Positive; DF, spirals	0 0 0 0		
72 30 yr.	1 yr.; Autisha	No past history of verruga; no actual signs or symptoms	Positive; coarse granular level; DF, no spirals	3 3 3 3 3 0	R. B. C. 3,360,000; hb. 7.25 Gm.	
127 35 yr.	Month of December 1939, Puente Challape; month of August 1941, Puente Challape; 1 mo. prior to present data, Puente Carrión	Blood cultures positive 3 mo. after sojourn at Puente Challape in August 1941; slight eruption on arms and legs of short duration; no signs or symptoms since	A: contaminated; B: positive by DF	A: 0 0 0 B: 0 0 0	A: hb. 9.9 Gm.; B: hb. 9.75 Gm.	Laboratory data: A end of month of last period of exposure, B about 1 wk. after end of same period

TABLE 7.—*Patients With Blood Culture Negative for B. Bacilliformis and Positive Agglutination Test, With or Without a Past History of Carrión's Disease*

Patient No.; Age	Duration and Place of Residence in Endemic Region	Clinical History, Signs and Symptoms	Agglutination Test (1 2 3 4 5 6)	Studies of the Blood	Comment
162 25 yr.	3 yr.; Santa Eulalia	2 yr. prior to present data, extensive miliary eruption present for 4 mo. preceded by 2 mo. of constitutional symptoms and arthralgia; no signs or symptoms at present	2 2 1	Hb. 10.25 Gm.	
68 43 yr.	Native of Canta	Verruga in childhood, with no details known; abdominal pain, anorexia, vomiting, loss of weight and irregular catamenia for 18 mo.	2 0 0	R. B. C. 2,000,000; hb. 5.25 Gm.; blood film quite suggestive of acute Oroya fever; no Bartonella	Seen in hospital; symptoms other than those of verruga; no diagnosis made; urobilin in stool (3+); stool benzidine +
65 20 yr.	Native of Matucana; 2 mo. in Huinco	Minimal eruption preceded by 8 days of fever at 6 yr. of age; no signs or symptoms since	2 1 1 0	Hb. 9.5 Gm.	
132 30 yr.	110 days; Puente Challape	Vague febrile symptoms and pains in bones during last week of period of exposure; no past history of verruga	3 1 0	Hb. 9.4 Gm.	Cultures contaminated; no gross evidence of growth of Bartonella
134 30 yr.	110 days; Puente Quita Sombrero, Puente Challape	No past history, signs or symptoms of verruga	3 3 2 1 0 0	R. B. C. 3,700,000; hb. 7.5 Gm.	Cultures contaminated; no gross evidence of growth of Bartonella
64 40 yr.	1 yr.; Huinco	No past history, signs or symptoms of verruga	3 2 1 0	R. B. C. 3,790,000; hb. 9 Gm.	

TABLE 8.—*Patients With Blood Culture Negative for B. Bacilliformis, Negative Agglutination Test, But With Actual Eruption, With or Without Constitutional Symptoms of Carrión's Disease*

Patient No.	Age, Yr.	Duration and Place of Residence in Endemic Region	Type and Duration of Disease
6	47	4 mo.; Autisha.....	Sparsely scattered nodular eruption; 3 wk.
11	39	1 yr.; Huaráz.....	B. bacilliformis reported in blood film 2 mo. prior to appearance of 1 nodule; no severe attendant illness
17	19	8 mo.; Huinco, Autisha	Three subcutaneous nodules, 2 mo.
20	31	8 mo.; Autisha.....	Small subcutaneous nodules, right shin; 1 mo.
22	38	4½ yr.; Barbablanca, Autisha	Miliary eruption, forearms and lower legs; 53 days
23	26	9 mo.; Autisha.....	Subsiding miliary eruption; 54 days
30	31	1 yr.; Huinco, Autisha, Barbablanca	Sparsely scattered nodules, with miliary eruption over both thighs; 2 mo.
35	18	7 mo.; Autisha.....	Three subcutaneous nodules; 6 mo.
38	48	11 mo.; Autisha, Huinco	One small red nodule, right wrist; 1 mo.
39	50	10 mo.; Autisha.....	Varied nodular eruption, face and legs; 6 mo.
47	19	4 yr.; Huinco, Autisha	Sparsely scattered small nodules; 2 mo.
71	28	10 mo.; Autisha.....	Minimal miliary eruption, extremities; 4 days
75	34	9 mo.; Huinco, Autisha	Several nodules, legs and arms; 2½ mo.
93	19	1 yr.; Huinco.....	Three definite subcutaneous lesions; 2½ mo.
96	42	8 mo.; Huinco.....	Moderate number of nodules, arms and legs; 8 days
97	26	3 mo.; Huinco.....	Moderate number of nodules, arms and legs; 26 days
98	37	1 yr.; Huinco	One or two subcutaneous nodules with numerous small nodules on forearms and lower legs and miliary eruption on arms and legs; 4 mo.
114	70	13 yr.; Santa Eulalia river valley	Subsiding generalized varied nodular eruption; 7 mo.
145	28	Life; San Jieronimo....	Evanescent miliary eruption over entire body; 1 yr.
176	17	137 days; Tornamesa, Surco, San Mateo	Extensive generalized nodular eruption on arms and legs, 1 mo.
186	27	4 mo.; Huinco, Autisha	Two subcutaneous nodules with generalized miliary eruption on arms and legs; 2 mo.
187	24	Life; Canta	Eruption; 103 days
185	20	1 mo. ending 5 mo. prior to present data; Yauyos	Generally scattered subcutaneous nodules; 5 mo.
198	22	3 mo. ending 7 mo. prior to present data; Surco	Jaundice and chills during 2d month of period of exposure; nodular eruption; 40 days

Average 3.5 yr.; maximum 28 yr.; minimum 30 days.

TABLE 9.—*Patients With a Past History of Carrión's Disease, With Blood Culture Negative for B. Bacilliformis and Negative Agglutination Test*

Patient No.	Duration of Residence in Endemic Region	Time Elapsed Since Termination of Disease	Type and Duration of Disease
1	21 days	126 days	Positive blood culture on 13th day of period of exposure; subsequent cultures negative
13	5 mo.	4 mo.	Positive blood culture; 1 wk. of evanescent eruption; subsequent cultures negative
16	7 yr.	5 yr.	Subcutaneous nodules; 2 mo.
18	3 yr. beginning 8 yr. prior to present data	6 yr.	Extensive generalized eruption; 6 mo.
21	1 yr.	58 days	Two subcutaneous nodules; 15 days
24	15 yr.	13 yr.	Generalized eruption; 3 to 4 mo.
26	2½ yr.	2 yr.	Large and small nodules; 2 mo.
31	6 yr.	6 yr.	Three small nodules; short duration
34	?	14 yr.	No details known
40	31 yr.	18 mo.	Moderately extensive eruption; 6 mo.
44	4 yr.	3 yr.	Moderately extensive rash, limited to legs; duration not known
46	7 yr.	6 yr.	Generalized eruption; duration not known
48	3 yr.	Since 1st attack: 12 yr. Since 2d attack: 5 yr. Since 3d attack: 1 yr.	All three eruptions miliary; duration not exactly known, though each attack self limited
52	7 yr.	11 yr.	One nodule; duration uncertain
53	8 yr.	5 yr.	Generalized miliary eruption; duration uncertain
55	6 yr.	6 yr.	Minimal eruption; duration uncertain
56	2 mo. 38 yr. prior to present data; for 7 yr. up to present	38 yr.	Generalized and varied eruption for 1 yr.
59	7 yr.	5 yr.	Minimal eruption; 6 mo.
78	3 yr. ending 5 yr. prior to present data	Since 1st attack: 8 yr. Since 2d attack: 7 yr. Since 3d attack: 5 yr.	1st attack: extensive varied eruption; 8 mo. 2d attack: similar to 1st; 4 mo. 3d attack: subcutaneous nodules
63	20 yr.	11 mo.	Miliary eruption over extremities; 2 mo.
82	4 yr. ending 8 yr. prior to present data	10 yr.	No details known
84	6 yr.	Since 1st attack; 5 yr. Since 2d attack: 4 yr.	1st attack: few subcutaneous nodules; 2 mo. 2d attack: miliary eruption; duration uncertain
86	1 yr.	5 mo.	Abundant miliary eruption; duration uncertain
87	8 yr.	7 yr.	Varied miliary and subcutaneous eruption; duration uncertain
88	3 yr. ending 4 yr. prior to present data and for 1 yr. up to present data	6 yr.	One subcutaneous nodule; duration uncertain
89	10 yr.	4 yr.	Varied eruption; 4 mo.
90	1 yr. ending 6 yr. prior to present data and for 1 yr. up to present data	7 yr.	Varied extensive generalized eruption; 1 yr.
92	29 yr.	6 yr.	Miliary and varied nodular eruption; 2 mo.
102	15 yr.	15 yr.	Miliary eruption on extremities; 1 mo.
103	13 yr.	5 yr.	Miliary eruption on trunk and leg; 1 mo.
106	23 yr.	Since 1st attack: 18 yr. Since 2d attack: 15 yr. Since 3d attack: 13 yr. Since 4th attack: 3 yr. Since 5th attack: 4 mo.	1st attack: severe generalized eruption; 1¼ mo. 2d attack: small nodules on legs and arms; 3 mo. 3d attack: 4 to 5 subcutaneous nodules; 6 mo. 4th attack: miliary eruption; 1 mo. 5th attack: moderate number of nodules; 6 mo.
107	13 yr.	12 yr.	Two to three eruptions on face and legs; each 2 to 3 mo.
108	7 yr.	5 yr.	Miliary eruption; 8 mo.
109	8 yr.	3 yr.	About 20 large nodules on both arms; 1 yr.
123	2 yr.	2 yr.	Generalized miliary eruption; 3 mo.
124	28 yr.	8 yr.	Subcutaneous nodules; 15 days
125	2 yr.	2 yr.	Abundant varied eruption on legs and arms; 2½ mo.
126	1 yr.	8 mo.	Small scattered nodules; 4 mo.
129	2 yr.	9 mo.	Extensive generalized eruption; 4 mo.
143	29 yr.	9 yr.	Moderately severe miliary eruption; 1 yr.
144	36 yr.	4 yr.	Scattered nodules; 1 mo.
147	20 yr. ending 20 yr. prior to present data	25 yr.	Generalized miliary eruption; 3 to 4 mo.
151	6 yr.	5 yr.	Miliary eruption; 3 mo.
152	42 yr.	24 yr.	Varied generalized eruption; 1 mo.
153	15 yr.	15 yr.	Miliary eruption; 3 mo.
154	1 mo. 12 yr. prior to present data and for 10 yr. up to present data	12 yr.	Generalized miliary eruption; 3 mo.
156	16 yr.	13 yr.	Miliary eruption on legs and arms; 6 mo.
157	30 yr.	29 yr.	No details recalled
158	12 yr.	10 yr.	Miliary eruption on face, arms and legs; 3 mo.
161	2 yr.	2 yr.	Minimal eruption; 6 mo.
170	5 yr.	5 yr.	Varied generalized eruption; 6 mo.
171	41 yr.	18 yr.	Minimal generalized miliary eruption; 2 to 3 mo.
172	9 yr.	7 yr.	Two subcutaneous nodules; 3 to 4 mo.
173	12 yr.	15 yr.	Minimal miliary eruption; 1 yr.
178	18 yr.	15 yr.	?Evanescent miliary eruption for 2 yr. prior to present data
201	7 yr.	1 yr.	Minimal eruption; duration uncertain
Average	11.5 yr.	5.9 yr.	
Maximum	42 yr.	38 yr.	
Minimum	21 days	58 days	

TABLE 10.—*Patients Resident in Endemic Regions With No Past History or Actual Evidence of Carrión's Disease, With Blood Culture Negative for B. Bacilliformis and Negative Agglutination Test*

Patient No.	Duration of Residence in Endemic Region	Patient No.	Duration of Residence in Endemic Region	Patient No.	Duration of Residence in Endemic Region
2	1 mo.	83	18 yr.	140	105 days
4	85 days	32	5 mo.	142	1 mo.
9	7 mo.	85	22 yr.	146	3 yr.
25	33 yr.	91	38 yr.	148	50 yr.
27	1 mo.	94	6 yr.	149	26 yr.
28	2 yr.	95	21 yr.	150	27 yr.
33	6 yr.	99	1 yr.	155	10 yr.
41	13 mo.	104	1 yr.	159	7 mo.
42	3 yr.	106	20 yr.	160	2 yr.
43	30 yr.	110	7 mo.	163	4 mo.
49	11 mo.	112	6 mo.	164	3 mo.
50	5 mo.	113	10 mo.	165	3 mo.
57	4 yr.	115	32 yr.	166	15 days
58	1 yr.	116	30 yr.	167	15 days
60	4½ yr.	117	24 yr.	169	8 yr.
62	1 yr.	119	14 yr.	193	3 mo.
67	36 yr.	120	15 yr.	199	4 mo.
69	5 mo.	130	105 days	202	10 mo.
76	3 mo.	133	114 days	203	43 days
79	1 yr.	137	47 days	Maximum	50 yr.
81	39 yr.	139	105 days	Minimum	15 days

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COMPARATIVE VALUE OF DIGITALIS AND OF OUABAIN IN THE TREATMENT OF HEART FAILURE

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To the careful reader of the medical literature of the United States it is a matter of no small surprise to find so many articles dealing with the pharmacology and clinical applications of digitalis, as contrasted with the small number of papers published on the strophanthins and especially on ouabain.

This same silence or oblivion is noted as one visits clinics and hospitals. Digitalis is not only the favorite but practically the sole drug employed in the treatment of heart failure,[1] whereas ouabain is looked on by specialists with disdain, and one might even add with distrust. Ouabain is generally considered to be imperfectly studied as regards its physiologic effects, uncertain in its clinical applications and dangerous in its results. At least, it is said that there is no reason for using ouabain when one has at hand such a sure agent as digitalis. This viewpoint was recently upheld by Gold,[2] who affirmed that there are no convincing proofs that intravenously administered strophanthin gives results which cannot otherwise be obtained by digitalis correctly handled.

This mental attitude toward ouabain is in frank disagreement with that held in European and Spanish-American countries, where the strophanthins, introduced into therapeutics by Fraenkel, and especially ouabain, recommended especially by Vaquez, are considered powerful weapons in the therapeutic arsenal against heart failure, for ouabain is as easy to manage and has been proved as safe as digitalis. It has its exact indications and its own field of application, and when limited to this field is capable of producing brilliant results, especially in those cases in which digitalis commonly gives poor ones or even fails completely.

A typical example of the European point of view is the following statement made by Vaquez:[3]

> There is hardly another drug which rests on so solid a basis as does ouabain, a well defined chemical product of known toxicity, the pharmacodynamic actions of which have been studied by investigators of the greatest competence; of precise indications, administration and posology, all of which are the result of innumerable and concordant clinical observations. Arnaud's ouabain . . . is the heroic remedy for acute or irreducible heart failure.

Similar statements have been made about strophanthin K (the product designated as strophanthin in the Pharmacopeia of the United States) by such authoritative

1. Luten, D.: The Clinical Use of Digitalis, Springfield, Ill., Charles C Thomas, Publisher, 1936. Levine, S. A.: Clinical Heart Disease, Philadelphia, W. B. Saunders Company, 1936. Leaman, W. G., Jr.: Management of the Cardiac Patient, Philadelphia, J. B. Lippincott Company, 1940. Fishberg, A. M.: Heart Failure, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 721.

2. Gold, H.: Recent Developments in Digitalis, Mod. Concepts Cardiovasc. Dis., 1942, vol. 12, no. 4.

3. Vaquez, H.: L'ouabaïne d'Arnaud, Arch. d. mal. du cœur **28**:773, 1935.

German clinicians as Romberg,[4] of Munich, and Edens,[5] of Düsseldorf, and about ouabain by such eminent pharmacologists as Schmiedeberg [6] and Tiffeneau.[7]

Such then are the two contrasting attitudes respecting ouabain, the one skeptical and the other enthusiastic. It is my belief that on scientific grounds there is no reason why such a discrepancy should continue to exist. A severe, critical study, both clinical and experimental, could rapidly and definitely confirm the excellence or the mediocrity of ouabain.

In Mexico and in the other Latin-American countries ouabain is employed regularly. I myself have used it extensively for the last twenty years, and in this paper I will try to summarize the impressions which as a clinician I have gathered from the use of it and to present in brief synopses, and by means of comparative charts, the different fields of application which I wish to review. The ouabain that I have employed has been prepared by Arnaud's method.

COMPARATIVE PHYSIOLOGIC ACTION

Digitalis and ouabain have similar physiologic actions. Both act fundamentally on the heart and only limitedly on the blood vessels. Both act partially through the vagus nerve and secondarily modify the circulation. But if the actions of the two are comparable, it does not follow that they are identical in every respect. Some physiologic mechanisms are more influenced by digitalis, while others are more influenced by ouabain.

Digitalis, as is well known, has a complex action on the myocardium. Certain functions are depressed, while others are stimulated. Digitalis depresses the activity of the auricular sinus, partly by direct action and partly by action of the vagus nerve, which results in a decrease in the number of heart beats, and it also depresses auriculoventricular conduction, which brings about a certain degree of blocking of the impulses descending from the auricle. On the other hand, it stimulates certain other functions of the heart. 1. It increases the irritability of the muscle fiber. 2. It increases its contractility, which is shown by the greater energy of the contraction. 3. It produces an increase in the general tone of the organ, which brings about a decrease in the size of the dilated heart.[8] From the influence of these combined actions there results, as Peters and Visscher [9] indicated, a greater efficiency in the work of the heart, which in turn gives, as Edens [10] pointed out, a better coronary blood supply.

Ouabain has these same physiologic actions but in varying degrees.[11] It depresses the automatism of the sinus and acts similarly on auriculoventricular conduction but to a lesser extent than digitalis. One frequently encounters a patient who has heart failure accompanied by tachycardia but who does not have

4. Romberg, E.: Tratado de las enfermedades del corazón y de los vasos, Barcelona, Edit. Labor, 1931.

5. Edens, E.: A. B. C. de la médication digitalique, Paris, Payot & Cie, 1938.

6. Schmiedeberg, cited by Romberg.[4]

7. Tiffeneau, M.: Étude pharmacologique et pharmacodynamique des glucosides strophantiques, Bull. d. sc. pharmacol. **29**:68, 1922.

8. In speaking of the tone of the heart, I do not ignore the fact that agreement regarding its strict physiologic significance is far from being unanimous. However, to us clinicians the tone of the heart has an objective reality, and its failure is shown by a dilatation of the chambers, by reason of the deficit in the heart's ability to resist distention.

9. Peters, H. C., and Visscher, M. B.: The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It, Am. Heart J. **11**:273, 1936.

10. Edens, E.: Die Digitalisbehandlung, Berlin, Urban & Schwarzenberg, 1934, p. 446.

11. Hazard, R.: Les médicaments cardiovasculaires: L'ouabaine, Paris, Centre de Documentation Universitaire, 1928.

arrhythmia (as may occur in hypertensive heart disease) and in whom under the influence of ouabain the cardiac failure is rapidly improved, but the tachycardia is not entirely corrected, rates higher than normal being maintained. It is also an equally common occurrence that in cases of fibrillation bradycardia produced by ouabain is much less accentuated than that resulting from the use of digitalis, which has a greater capacity for blocking the conduction system. It can, therefore, be stated that in those cases in which the action sought is depression of the conduction path, ouabain is decidedly inferior to digitalis in results obtained.

In contrast to its limited depressor action just mentioned, ouabain has a markedly stimulating effect on other functions of the myocardium; that is, the fundamental action of ouabain is expressed not in terms of the functions which it depresses but rather in terms of the myocardial functions which it stimulates. The contractility and the tone of the striated muscle fibers are considerably reenforced, which results in a distinct increase in the energy of systolic contraction and an appreciable reduction in the size of the heart. These two effects of ouabain represent the dominant characteristics of its action, and both are notably superior to those obtained with digitalis.

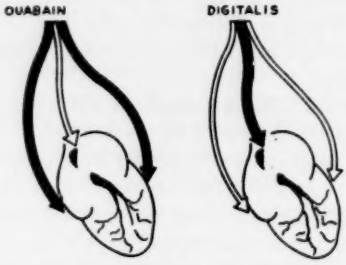

Fig. 1.—Graphic representation of the differences in the action of ouabain (stimulation of myocardial functions) and digitalis (depression of functions of the neuromuscular fibers).

Figure 1 permits one to appreciate these differences objectively. Compared with ouabain, digitalis has a predominant action on the excitoconductor system, this is to say, on the differentiated, or neuromuscular, fibers, the functions of which it depresses (chronotropism and conduction). Compared with digitalis, ouabain has a preponderant action on the striated, contractile fiber of the myocardium, the functions of which it stimulates (contractility and tonicity).

These facts stand out with equal clarity in figure 2, in which one can appreciate the pronounced increase in the amplitude of the ventricular contractions of a frog's heart, greater with ouabain than with digitalin, as well as the notably greater increase in tone when ouabain is given.

Figure 3 indicates the accentuated decrease in the size of a frog's heart when it is subjected to the action of ouabain, which is a reliable indication of a pronounced increase in tone. Digitalis does not ordinarily produce such wide variations.

Apart from their action on the heart itself, digitalis and ouabain have an inconstant effect on the arteries and the blood pressure. It is well known that though animals experimentally undergo an elevation in blood pressure, in human beings during periods of heart failure and under efficient but nontoxic dosage of these drugs no definite variations in blood pressure are noted. In some cases it remains unchanged; in others it is slightly diminished, and in still others there is a

moderate elevation of systolic pressure, combined or not with a lowering of diastolic pressure. It is generally accepted that in human beings nontoxic doses either of digitalis or of ouabain are not hypertensive and that when hypertension is observed it is always moderate, is cardiac and not arteriolar in origin and is restitutional in type; that is to say, it brings about a recuperation of the pressure rates, which had previously been lowered during the course of heart failure. And as far as the restoration of blood pressure is concerned, ouabain ordinarily produces greater elevations than digitalis, since it has a more intensive action on the contractile energy of the heart, as has just been mentioned.

Figure 4 outlines the commonly observed action of ouabain in the course of hypertensive heart failure.

There are, furthermore, two fundamental differences between digitalis and ouabain:

1. Digitalis and its glucosides are administered preferably by the oral route. Their absorption by way of the intestinal mucosa contributes toward their fixation

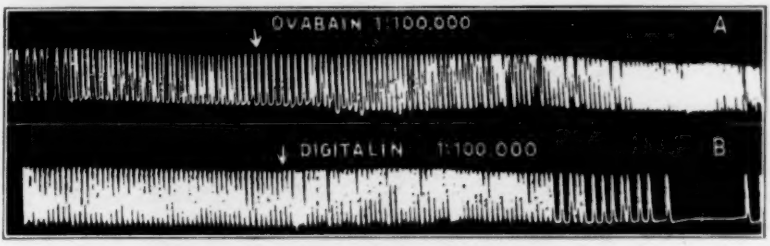

Fig. 2.—The effect of ouabain and digitalis on the amplitude of the ventricular contractions of a frog's heart. The isolated hearts of male frogs weighing 40 Gm. (*A*) and 35 Gm. (*B*) were employed.

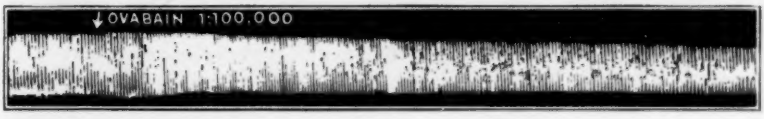

Fig. 3.—The accentuated decrease in the size of a frog's heart, a reliable indication of a pronounced increase in tone, when it is subjected to the action of ouabain. The isolated heart of a male frog weighing 35 Gm. was employed.

on the heart at a slow rate. The action of digitalis begins to manifest itself one or two hours after administration, takes twenty-four hours to produce frank effects and requires forty-eight to seventy-two to reach its maximum.[12]

Ouabain, on the other hand, is largely hydrolyzed in the intestine, which renders uncertain its absorption by the oral route. On the contrary, its complete solubility in water permits one to inject it intravenously with ease. It requires only a few seconds to fix itself on the myocardium; its therapeutic action is observed before five minutes, reaches its greatest intensity in one hour and in twenty-four hours has disappeared.

2. Digitalis is an accumulative drug. In order to insure complete impregnation of the myocardium and to obtain a maximum effect, a dose six to ten times greater than the amount of digitalis destroyed in one day must be administered. When administration is discontinued the myocardium gradually uses

12. Chávez, I.: La digitalina, Tesis recepcional, Universidad Nacional, México, 1920.

up the drug received, which prolongs its effect for six, eight and ten days after the last dose, on the condition, of course, that it was in reality a useful dose.

Ouabain, on the contrary, does not accumulate. The dose at which the myocardium becomes saturated, that is, the one which affords the maximum effect, is the same as the dose destroyed in one day. When administration of the drug is discontinued its effects disappear in twenty-four to thirty-six hours. Only after a long series of injections (six to ten) can it barely be observed that the drug requires from forty-eight to seventy-two hours for its complete destruction.

In the other aspects of their use, digitalis and ouabain do not reveal any fundamental differences, except for those which vary in degree, by reason of their inherent characteristics. Consequently, they have the same generic action on heart failure; they produce the same changes on the ST segment and the T wave of the electrocardiogram; they have the same group of contraindications, and they produce identical signs of intoxication.

CLINICAL APPLICATIONS AND SELECTION OF THE SEPARATE FIELDS OF ACTION OF DIGITALIS AND OUABAIN

On keeping in mind the similarities and differences which have just been indicated, the separation between the two fields of action of digitalis and ouabain

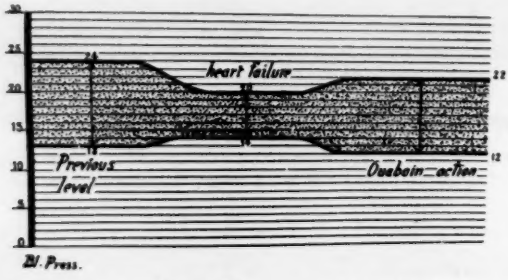

Fig. 4.—The action of ouabain in the course of hypertensive heart failure.

seems quite logical. Let me express as comprehensively as possible the criteria which should guide one in the selection of cases:

1. Since ouabain has a rapid and intensive effect, its field comprises acute heart failure, or rather, the acute accidents of heart failure; paroxysmal nocturnal dyspnea, and attacks of acute pulmonary edema in persons suffering from failure of the left ventricle. However, not only do these advanced clinical pictures fit into its field of action, but their threatening stages as well, when it is legitimate to suppose that the effect of digitalis would not be exerted in time to dispel the danger.[13]

2. Since digitalis acts preponderantly by inhibiting the auricular sinus and by blocking the auriculoventricular bundle, its ideal field of action is in congestive heart failure, with pronounced tachycardia and particularly with auricular fibrillation. Usually, digitalis is ideal for use in rheumatic heart disease and chronic valvular lesions in young persons. In this field digitalis reigns supreme, and its results are spectacular.[14]

13. Vaquez, H.: Médicaments et médications cardiaques, Paris, J. B. Baillière et fils, 1925. Laubry, C.: Maladies du cœur et des vaisseaux, Paris, Gaston Doin, 1930, vol. 3.

14. Stroud, W. D.: Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, 1940. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937.

3. Not only in acute heart failure, but in chronic failure of the left side of the heart as well, with or without congestive manifestations (fibrillation is usually lacking and tachycardia is moderate but enlargement of the heart, gallop rhythm, alternation of the pulse and a lowering of blood pressure are present), does ouabain assume first place. This is the common meeting ground for persons suffering from failure of the left side of the heart, chronic coronary insufficiency, long established hypertension and complicated syphilitic aortitis. Here it is that ouabain finds its greatest indications, strengthening systolic activity, diminishing diastolic dilatation, restitutionally increasing blood pressure and secondarily improving coronary circulation. This does not imply that digitalis is impotent to better this clinical picture; I only wish to affirm that its results are inferior when there is neither tachycardia nor fibrillation to be corrected, since it has less reenforcing action on the contractile fiber.

4. Once heart failure is under control, whatever its type, and when a prolonged sustaining treatment is to be maintained, digitalis is the drug of choice. The facility of determining the daily dose, the ease of oral administration and the sustained constancy of its effects make it quite superior to ouabain in prolonged treatments. The same can be said for prolonged sustaining treatments in cases of auricular fibrillation when the object is to hold down the ventricle to moderate rates. The supremacy held by digitalis here is indisputable.[15]

There still remain other more limited fields of application, of which some can be reserved for digitalis and others for ouabain. Suffice it for the purposes of this general view of the subject to summarize the four fundamental headings which have just been outlined by stating that digitalis is the ideal remedy in cases of congestive heart failure with tachycardia, specially with auricular fibrillation; in those cases in which fibrillation is a permanent feature but in which heart failure is not ostensibly present, and in unstable cases of heart failure in which prolonged sustaining cure is desired. Ouabain, on the other hand, is the heroic remedy for the acute phenomena of failure of the left ventricle, as it is also the remedy of choice for chronic failure of the left side of the heart in persons suffering from coronary arteriosclerosis, long established hypertension and aortitis.

In observing these fields more closely, one sees that the clinical pictures reserved for digitalis are those which commonly develop in children and in adults, in persons with chronic valvular disease and in patients with rheumatic heart disease more than in any others; that ouabain will be more frequently used for treating patients in the second half of life, aged persons and, above all, persons with vascular disease, coronary arteriosclerosis, hypertension, syphilis and cardiorenal disease.

The fact that digitalis when employed in the treatment of aged persons frequently gives poor results, at least ones not as satisfactory as those obtained in young persons, has already struck the attention of clinicians, and Willius[16] has recently enlarged on this view. The fact is certain, and the explanation is the one I have offered here. Heart failure in aged persons, commonly vascular in origin, responds much better to ouabain than to digitalis.

It is obvious, of course, that the fields of application of the two drugs are not always as clear as I have sketched them here. In children there are certain types of heart failure, with considerable cardiomegaly and moderate tachycardia, in which ouabain can better act on a greatly dilated, but rhythmic ventricle, and there are certain patients with coronary disease and failure of the right and the

15. Chávez, I.: El campo de manejo de la digital, Arch. latino am. de cardiol. y hemat. **10**:101, 1940.

16. Willius, F. A.: El uso racional de la digital, Arch. latino am. de cardiol. y hemat. **5**:33, 1935.

left side of the heart, largely congestive in nature, and with auricular fibrillation, to whom digitalis can be more useful. In other cases, the successive use of both drugs will be the rational treatment: first, ouabain, in order to correct the more striking accidents of heart failure, and later, digitalis, to control tachycardia and fibrillation. In this way, as Vaquez [3] and Edens [5] have pointed out, the initial administration of ouabain often has a reactivating effect which permits digitalis to render its maximum of efficiency.

TECHNIC OF THE ADMINISTRATION OF OUABAIN

I personally have used strophanthin K rarely. I have however, been using ouabain (prepared by Arnaud's method) extensively for the last twenty years, and all that has been said in this paper refers to it alone. Of it I can say that when correctly handled, I have never seen in thousands of patients treated one single death which could be attributed to it. It is known that the same cannot be said for strophanthin K.

But, as I have said, it is absolutely essential to handle ouabain correctly, and to that end it should be remembered that the margin of safety between the useful and the toxic dose is narrow, while with digitalis it is rather wide. Successful treatment depends on remaining within the vicinity of the useful dose, rather than approaching the limits of the toxic dose. More than 0.5 mg. of ouabain per day should be considered a toxic dose, such as those recommended by Danielopolu and those employed by Wyckoff and Goldring.[17] Easily toxic as well is such a daily dose if it is administered over a period of several days. Vaquez [3] recommended two injections of 0.25 mg. on the first day and a single injection on each of the two succeeding days, or a total of 1 mg. in three days.

As for myself, I have been accustomed to give a dose of 0.25 mg. per day for six days by the intravenous route exclusively. This series of six doses can be shortened if the patient begins to show signs of intolerance or can be lengthened to eight or ten, according to the benefit derived. Only exceptionally have I had to prescribe two doses on a single day of the series.

As a general rule, one series of injections of ouabain is sufficient to control overwhelming heart failure. Patients who suffer from long nights of insomnia and from the torment of dyspnea and crises of asthma, sleep like children once again after the first injection, or at most, after the second or the third one. Patients who have resisted digitalis rapidly recover under the action of ouabain. Its effect on nocturnal dyspnea in patients with cardiac disease is comparable only to that of morphine.

Once the series of injections of ouabain has been concluded, one can, if it is deemed necessary, continue treatment with digitalis. No interval of waiting is required, as ouabain is not a drug which tends to accumulate. On the other hand, when one wishes to change from digitalis to ouabain, it is imperative to wait a few days, according to the dose of digitalis administered.

Ouabain can be given for months and even years, when required, without variation in the dose needed or in the potency of its action. In an aged, overweight physician with coronary arteriosclerosis and massive heart failure in whom death seemed imminent and for whom therapy with digitalis had proved useless, I was able to sustain a cure with ouabain for two and a half years, with no greater

17. Wyckoff, J., and Goldring, W.: Intravenous Injection of Ouabain in Man, Arch. Int. Med. **39**:488 (April) 1927.

interruption then two days a week. During those two and a half years the patient was able to carry on a subnormal life and even found it possible to resume moderately the practice of his profession.

SUMMARY AND CONCLUSIONS

In the face of the divergence of opinion about the value of ouabain in the treatment of heart failure, the comparative actions of digitalis and of ouabain are outlined and the results of twenty years' experience in the use of ouabain are set forth.

Digitalis and ouabain have similar, but not identical, action on the decompensated heart. By way of comparison, digitalis exerts a more pronounced effect on the functions of sinus excitation and auriculoventricular conduction, which it depresses; ouabain, on the contrary, acts primarily on contractility and tonicity, which it stimulates.

Comparatively speaking, digitalis directs its chief effect on the differentiated, neuromuscular tissue of the heart; ouabain, on the undifferentiated, contractile fibers of the myocardium.

Digitalis, administered by the oral route, fixes itself slowly on the heart; ouabain, administered intravenously, acts with rapidity. The maximum effect of digitalis is reached in two or three days, whereas that of ouabain is reached in one or two hours. Digitalis accumulates; ouabain does not. On discontinuing the drug, digitalis extends its effects over a period of several days, up to eight or ten; those of ouabain disappear in twenty-four to thirty-six hours.

The best fields for the application of digitalis are congestive heart failure with tachycardia and specially with auricular fibrillation, fibrillation even in the absence of heart failure and long sustaining treatment of patients with slightly decompensated cardiac disease.

The best fields for the application of ouabain are the acute phenomena of failure of the left ventricle and chronic failure of the left side of the heart in patients with vascular disease, such as coronary arteriosclerosis, hypertension and syphilitic aortitis.

I recommend, as the best technic for the use of ouabain, one intravenous injection daily of 0.25 mg. in a series of six doses and more according to the tolerance of the individual patient and the clinical improvement obtained. In thousands of patients treated over a period of twenty years I have not encountered a single case of death attributable to ouabain.

211 Paseo de la Reforma.

INVOLVEMENT OF THE LIVER IN DISEASE OF THE GALLBLADDER

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Although the clinical demonstration of hepatic damage in cholecystic disease is of great importance in the medical and surgical management of disease of the biliary tract, there is little definite knowledge of this subject recorded in the literature. Studies of the incidence of hepatic involvement in disease of the gallbladder have not been conclusive and have not clarified the relationship between the two diseases. The purpose of this paper is to present new evidence of hepatic injury in disease of the gallbladder as detected by a simple laboratory method.

The presence of hepatic damage in disease of the gallbladder has been explained in three ways. One group of investigators [1] have stated the belief that the gallbladder is the primary source of infection and that the liver is involved by direct extension. Others have postulated that the liver acts as a bacterial filter of the body and is the chief source of the infection, involving the gallbladder secondarily by way of the bile ducts and lymphatics.[2] A third group of workers [3] have maintained that the pathologic changes in the liver and those in the gallbladder are completely independent of each other.

After Riedel [4] in 1888 first demonstrated enlargement of the right lobe of the liver in cholecystitis, no critical work appeared until 1918, when Graham [5] described the pathologic involvement of the liver in 30 patients with disease of the biliary tract. Biopsy specimens taken at operation showed microscopic evidence of inflammation of the liver in 87 per cent of the patients with acute and subacute cholecystitis. MacCarty and Jackson [6] studied the liver histologically in 58 patients with acute, subacute and chronic cholecystitis and demonstrated hepatic disease in 81 per cent. They could find no apparent relationship between the severity of the hepatic disease and the degree of inflammation of the gallbladder.

From the Department of Medicine, the University of Chicago.

1. Koster, H.; Goldzieher, M. A., and Collens, W. S.: The Relation of Hepatitis to Chronic Cholecystitis, Surg., Gynec. & Obst. **50**:595, 1930. Else, J. E.; Rosenblatt, M. S., and Davis, A. M.: The Relationship of Hepatitis to Cholecystitis, Northwest Med. **29**:252, 1930.

2. Tietze, A., and Winkler, K.: Die Beteiligung des Leberparenchyms an der Gallensteinkrankheit, Arch. f. klin. Chir. **129**:1, 1924. Genken, I.: Pathologisch-anatomische Veraenderungen in Leber und Gallenblase bei chronischer Cholecystitis ohne Steine, ibid. **144**:752, 1927. Hadley, M. N.: Liver Pathology and Physiology and Its Relation to Diseases of the Gall Bladder, J. Indiana M. A. **20**:293, 1927.

3. (*a*) Martin, W.: Hepatitis and Its Relation to Cholecystitis, Ann. Surg. **85**:535, 1927. (*b*) Noble, J. F.: The Relation of Hepatitis to Cholecystitis, Am. J. Path. **9**:473, 1933.

4. Riedel: Ueber den zungenförmigen Fortsatz des rechten Leberlappens und seine pathognostische Bedeutung für die Erkrankung der Gallenblase nebst Bermerkungen über Gallensteinoperationen, Berl. klin. Wchnschr. **25**:577, 1888.

5. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521, 1918.

6. MacCarty, W. C., and Jackson, A.: The Relation of Hepatitis to Cholecystitis, Minnesota Med. **4**:377, 1921.

Judd in 1921 observed hepatitis at autopsy with infections of the gallbladder and biliary tract but never with peptic ulcer or appendicitis.[7] In 1924, however, Heyd, MacNeal and Killian,[8] investigating the incidence of hepatic disease in association with appendicitis and cholecystitis, found it as frequently with the former as with the latter. The degree of hepatic involvement was proportional to the chronicity of the infection. Mentzer [9] in 1926 made detailed postmortem studies of 548 patients with disease of the gallbladder. Sections for microscopic study were taken from the liver adjacent to the gallbladder and from the dome of the right and of the left lobe of the liver. The liver almost always showed hepatitis adjacent to the gallbladder, while sections taken from the left lobe were essentially normal even in patients with severe cholecystitis and cholelithiasis. Mentzer found that in 60 to 70 per cent of his patients there was pathologic evidence of hepatitis at postmortem examination regardless of the presence or absence of cholecystic disease. Noninflammatory lesions, including cholesterosis of the gallbladder, were associated with hepatitis in 97 per cent.

Noble [5b] studied the livers and gallbladders microscopically in 212 unselected autopsies. All but 5 of the subjects showed inflammatory cellular infiltration of the liver, although a large number had no evidence of disease of the gallbladder and none had clinical evidence of cholecystitis. Colp, Doubilet and Gerber [10] made an intensive study of the liver in patients with acute and chronic cholecystitis, using special stains and taking specimens for biopsy deep in the parenchyma of the right and left lobes of the liver. They concluded that the periportal cellular infiltration observed in disease of the biliary tract is not specific and that there is no evidence that hepatitis is associated with cholecystic disease in the absence of jaundice. They observed focal cellular degeneration in the presence of jaundice and attributed these changes to bile stasis rather than to a primary disease of the gallbladder.

Although the majority of writers feel that there is a direct relationship between cholecystitis and hepatitis and that long-standing cholecystic disease leads to progressive damage to the liver, the evidence cited indicates that there are conflicting opinions as to the significance of mild cellular changes in the liver and that microscopic studies alone may not demonstrate conclusively significant disease and abnormal function of the liver.

Because of the liver's multiplicity of function and large margin of reserve, the ideal laboratory test for its functional capacity is difficult to achieve. Tests of hepatic function in the past have not been sensitive enough to detect early involvement of the liver in cholecystic disease or have been too complicated to permit collection of a large series of cases. The bromsulphalein test, for example, cannot be evaluated in the presence of jaundice, and consequently its value in the study of disease of the gallbladder is limited. Of Cantarow's [11] series of 49 patients with acute cholecystitis, 41 had a normal serum bilirubin content and only

7. Judd, E. S.: Relation of the Liver and Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197 (July 16) 1921. Judd, E. S.; Nickel, A. C., and Wellbrock, W. L. A.: The Association of the Liver in Disease of the Biliary Tract, Surg., Gynec. & Obst. **54**: 13, 1932.

8. Heyd, C. S.; MacNeal, W. J., and Killian, J. A.: Hepatitis, in Its Relation to Inflammatory Diseases of the Abdomen, Am. J. Obst. & Gynec. **7**:413, 1924.

9. Mentzer, S. H.: A Clinical and Pathological Study of Cholecystitis and Cholelithiasis, Surg., Gynec. & Obst. **42**:782, 1926.

10. Colp, R.; Doubilet, H., and Gerber, I. E.: The Relation of Cholecystitis to Pathological Changes in the Liver, Ann. Surg. **102**:202, 1935.

11. Cantarow, A.: Hepatic Function: I. Noncalculous and Calculous Cholecystitis, Arch. Int. Med. **54**:540 (Oct.) 1934; The Van Den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, Am. J. M. Sc. **184**:228, 1932.

5, or 12.2 per cent, of these had an abnormal bromsulphalein retention. A similarly low incidence of hepatic involvement was found in 244 patients with chronic cholecystitis without gallstones and in 88 patients with calculous cholecystitis whose serum bilirubin determinations were normal. Abnormal bromsulphalein retention occurred in 32, or 13 per cent, of the first group and in 11, or 12.5 per cent, of the second.

Quick,[12] in his original application of the hippuric acid excretion test to human beings, performed the test on 6 patients with disease of the biliary tract and found the liver normal in 4. Kohlsteadt and Helmer[13] found an abnormally low excretion of hippuric acid in 11 of 21 patients. The patients with normal excretion of hippuric acid made an uneventful recovery after cholecystectomy, while those with impaired hepatic function had a turbulent postoperative course or died of hepatic insufficiency, according to the degree of damage to the liver. Pohle and Stewart,[14] using the cephalin-cholesterol flocculation test, found 3 mildly positive reactions in 30 patients with chronic cholecystitis with or without gallstones, while 8 of 11 patients with a stone in the common duct gave positive reactions. Recently Mateer and co-workers[15] found impaired hepatic function in over 50 per cent of 67 patients with proved cholelithiasis by use of the intravenous hippuric acid, the cephalin-cholesterol and the colloidal gold test.

The controversial evidence presented by pathologists and by investigators studying hepatic function in cholecystic disease led us to make a further study of the incidence of hepatic involvement in disease of the gallbladder.

METHODS AND RESULTS

The colloidal gold test of the serum for hepatic disease[16] seemed particularly suitable for this study because of its marked sensitivity and because it permits of a large number of studies. The reaction was found positive by one of us[16] in over 90 per cent of 96 patients with hepatic disease, and the unusual sensitivity of the test has been confirmed by Loew and Noth[17] and by Mateer and co-workers,[15] who found that the reaction was positive in 21 per cent more patients than the reaction to the cephalin-cholesterol flocculation test in a study of 124 patients with disease of the liver. In some instances the colloidal gold test has indicated hepatic disease which was not demonstrable by other laboratory methods but was later confirmed by autopsy, biopsy or the consequent clinical course of the patient. Sweet, Gray and Allen[18] found it most sensitive in detecting hepatic involvement in hepatolenticular degeneration. False positive reactions have occurred in less than 5 per cent of 400 normal control patients whom we have studied.

12. Quick, A. J.: The Synthesis of Hippuric Acid: A New Test of Liver Function, Am. J. M. Sc. **185**:630, 1933.

13. Kohlsteadt, K. G., and Helmer, O. M.: A Study of the Hippuric Acid Excretion as a Test of Hepatic Function, Am. J. Digest. Dis. & Nutrition **3**:459, 1936.

14. Pohle, F. J., and Stewart, J. K.: The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, J. Clin. Investigation **20**:241, 1941.

15. Mateer, J. G.; Baltz, J. I.; Marion, D. F.; Hollands, R. A., and Yagle, E. M.: A Comparative Evaluation of the Newer Liver Function Tests, Am. J. Digest. Dis. & Nutrition **9**:13, 1942.

16. Gray, S. J.: The Colloidal Gold Reaction of Blood Serum in Diseases of the Liver, Arch. Int. Med. **65**:524 (March) 1940.

17. Loew, E. R., and Noth, P.: Hepatic Dysfunction in Relation to the Reaction Between Blood Serum and Colloidal Gold, Am. J. Physiol. **133**:P 364, 1941.

18. Sweet, W. H.; Gray, J. S., and Allen, J. G.: Clinical Detection of Hepatic Disease in Hepatolenticular Degeneration, J. A. M. A. **117**:1613 (Nov. 8) 1941.

The test requires only 0.1 cc. of blood serum and is not affected by abnormal concentrations of serum bilirubin or blood lipids. Serum from patients with hepatic disease when properly diluted flocculates the colloidal gold solution, giving a syphilitic curve similar to that obtained with syphilitic spinal fluid. We believe that the flocculation of the colloidal particles depends on qualitative changes within the globulin fractions of the blood.

The colloidal gold test was performed on 100 patients with disease of the gallbladder confirmed by roentgenogram or surgical intervention. Ninety-seven of these patients had gallstones proved by one or both of these methods. There were 92 women and 8 men; their ages varied between 20 and 70 years, with an average of 43 years. A careful history was taken to determine the duration of the disease, the degree and duration of jaundice, previous episodes of jaundice and other symptoms and the presence of fever and chills. Special inquiry was made into such predisposing factors to disease of the liver as the use of drugs (cinchophen, arsenicals, etc.) and previous catarrhal jaundice, syphilis, alcoholism, vitamin deficiencies, etc.

The 100 patients with proved disease of the gallbladder were classified into four groups according, first, to the past or present history of jaundice (or an elevated serum bilirubin determination) and, secondly, to the clinical evidence of infection of the gallbladder, such as fever, chills or leukocytosis. These four distinct groups, comprised (1) patients having jaundice with infection, (2) those having jaundice without infection, (3) those having infection without jaundice and (4) those having quiescent disease of the gallbladder (no jaundice or infection). The term "infection" is used in the clinical sense, to denote a history of fever or chills at any time in the disease process or the presence of leukocytosis or fever. Care was taken to exclude patients with inadequate histories or insufficient hospital studies. The first two groups had stones in the common duct with jaundice and the last two groups had stones in the cystic duct or within the gallbladder. The fourth group, classified as having quiescent disease of the gallbladder, gave no history of previous jaundice or chills and fever. Determinations of the serum bilirubin were normal, and there was no fever or leukocytosis during an adequate period of study. Some of the patients complained of vague abdominal distress, while others were asymptomatic, and the discovery of gallstones on roentgen examination was an incidental finding in many instances.

A positive reaction to the colloidal gold test, indicating hepatic disease, was found in 46 of 100 patients with disease of the gallbladder (table 1). There were 51 patients who were jaundiced or presented clinical evidence of acute cholecystitis, i. e. fever and leukocytosis. Evidence of disease of the liver was found in 55 per cent of these patients. The incidence was highest in the patients with jaundice and infection. Ten of the 17 patients (58.8 per cent) in this group gave a positive reaction to the colloidal gold test. Jaundiced patients without clinical evidence of infection of the gallbladder showed a slightly lower incidence of damage to the liver, 10 of the 19 patients (52.5 per cent) giving a positive reaction to the colloidal gold test. Patients with acute cholecystitis (fever, chills and leukocytosis) and no jaundice revealed the same incidence of hepatic involvement as those with jaundice and no clinical evidence of infection. In this group 8 of the 15 patients (53.3 per cent) presented a positive reaction to the colloidal gold test.

The incidence of hepatic damage was definitely lower in the group of patients with quiescent disease of the gallbladder. Only 18 of the 49 patients (36.7 per cent) in this group had hepatic involvement as determined by the colloidal gold test, in contrast to over 50 per cent in the groups with jaundice or infection.

It is evident that jaundice or infection of the gallbladder or both are associated with disease of the liver in a large number of patients. Since the duration of the jaundice or infection and repeated exacerbations and recurrences of the disease over a period of years might be important factors in producing hepatic damage, we studied the incidence of disease of the liver in relation to the duration of these symptoms. Although a further subdivision of these studies results in a

TABLE 1.—*Incidence of Positive Reactions to the Colloidal Gold Test in Patients with Disease of the Gallbladder*

	Number of Patients	Incidence of Positive Reactions to Colloidal Gold Test			
		No.	%	No.	%
A. Jaundice with infection	17			10	58.8
1. Duration of symptoms					
(*a*) 1 to 7 days	8	3	37.5		
(*b*) 5 weeks	4	2	50.0		
(*c*) 2 or more months	5	5	100.0		
B. Jaundice without infection	19			10	52.5
1. Duration of symptoms					
(*a*) 1 month	4	0			
(*b*) 1 to 5 years	11	7	63.0*		
(*c*) 5 to 10 years	4	3	75.0		
C. Infection without jaundice	15			8	53.3
1. Duration of symptoms					
(*a*) 1 week	3	1	33.3		
(*b*) 1 to 2 months	6	3	50.0		
(*c*) 1 to 3 years	6	4	66.6		
D. Quiescent disease of gallbladder (no fever or jaundice)	49			18	36.7
1. Duration of symptoms					
(*a*) 6 months to 1 year	18	11	61.1		
(*b*) 2 to 5 years	16	4	25.0		
(*c*) 5 or more years	15	3	20.0		
Total patients studied	100			46	46.0

TABLE 2.—*Bacterial Flora of the Gallbladder and Bile*

	Number of Patients	Incidence of Positive Reactions to Colloidal Gold Test	
		No.	%
A. Growth	14	7	50
B. coli 5			
Pneumococcus of type III 1			
Str. haemolyticus 2			
Str. viridans 1			
Staph. albus 1			
Ps. pyocyanea 1			
B. typhosus 1			
B. welchii 1			
Diphtheroids 1			
B. No bacterial growth	8	2	25

relatively small number of cases in each group, we feel that there is sufficient evidence to indicate that the duration of disease of the biliary tract is an important factor in producing hepatic damage.

The incidence of disease of the liver increased with the duration of the symptoms in the 17 patients with jaundice and infection of the gallbladder (table 1). Hepatic damage was demonstrable in 37.5 per cent of patients whose symptoms were of one week's duration or less, in 50 per cent of patients with symptoms of five weeks' duration and in 100 per cent of patients with jaundice and infection of more than two months' duration.

TABLE 3.—*Symptomatology, Bacteriology and Pathology of Disease of the Gallbladder*

Patient	Symptoms	Duration	Bacterial Flora of Gallbladder and Bile	Pathologic Changes in Gallbladder	Pathologic Changes in Liver	Reaction to Colloidal Gold
1. A. G.	Recurrent chills, fever and jaundice	6 yr.	B. coli, pneumococcus of type III, Str. haemolyticus	Extensive fibrous and round cell infiltration; chronic cholecystitis and cholelithiasis	Cholangitis and biliary cirrhosis (autopsy)	Strongly positive
2. B. V.	Recurrent chills, fever and jaundice with colic	10 yr.	B. coli, Pseudomonas pyocyanea, Str. viridans	Round cell infiltration, erosions and hypertrophy; chronic cholecystitis and cholelithiasis	Periductal and intralobular round cell infiltration; early fibrosis, fatty infiltration	Strongly positive
3. R. B.	Chills, fever, jaundice, colic (mild diabetes mellitus and obesity)	10 days	B. coli	Gangrenous cholecystitis; cholelithiasis	Marked fatty infiltration; mild lymphocytic infiltration; vacuolation of liver cells	Positive
4. S. P.	Recurrent colic, chills and fever; no history of jaundice	10 mo.	No growth	Acute cholecystitis, edema and thickening of gallbladder wall, hemorrhages, round cell infiltration and denuded mucosa; cholelithiasis	.....	Positive
5. A. B.	Recurrent colic; no fever, chills or jaundice	6 mo.	No growth	Thickened muscularis, round cell infiltration; cholelithiasis	.....	Positive
6. T. M.	Recurrent colic, fever, chills and jaundice	6 yr.	Str. haemolyticus, Staph. aureus, Str. viridans	Chronic cholecystitis and cholelithiasis; cicatricial stenosis of common duct	Biliary cirrhosis of liver	Strongly positive
7. B. K.	A. Colic, chills, fever and jaundice	3 wk.	B. coli, Str. viridans	Minimal round cell infiltration, small erosions, fibrosis of walls of gallbladder; cholelithiasis	.....	Negative
	B. Postoperative colic, jaundice and fever	5 wk.	B. coli	Choledocholithiasis; dilatation of common duct	.....	Positive
8. C. R.	Pain in right upper quadrant; no jaundice, fever or chills	10 yr.	No growth	Minimal round cell infiltration and fibrosis; one stone in cystic duct of gallbladder	.....	Negative
9. T. S.	Recurrent fever and chills	1 mo.	.....	Empyema of gallbladder and cholelithiasis	.....	Positive
10. D. S.	Recurrent colic, jaundice, fever and chills	5 yr.	.....	Cholelithiasis; large stone in common duct; dilated common and cystic ducts	Nodules in liver suggesting biliary cholesterosis; dilated hepatic ducts	Positive
11. A. G.	Recurrent colic; no fever, chills or jaundice	4 mo.	.....	Cholelithiasis; adenocarcinoma of gallbladder	Adenocarcinoma of liver adjacent to gallbladder	Positive
12. A. M.	Recurrent epigastric pain; no jaundice, fever or chills	5 mo.	No growth	Adenocarcinoma of gallbladder; cholelithiasis; round cell infiltration and fibrosis	No metastases to liver	Negative
13. C. D.	Vague abdominal distress; occasional pain in right upper quadrant	10 yr.	No growth	Minimal cellular infiltration, small mucosal erosions, cholelithiasis	.....	Negative
14. A. K.	Vague abdominal distress	20 yr.	No growth	Minimal round cell infiltration, fibrosis, cholelithiasis	.....	Negative
15. L. H.	Recurrent colic; no jaundice or fever	9 mo.	Str. viridans	Marked round cell infiltration, hemorrhages, mucosal erosions; cholelithiasis	.....	Positive

The same increase in the incidence of hepatic damage with time was noted in the 19 patients with jaundice but without clinical or laboratory evidence of infection of the gallbladder (table 1). The patients with intermittent jaundice of one month's duration without concomitant evidence of infection of the gallbladder revealed no incidence of hepatic damage; intermittent jaundice over a period of one to five years caused hepatic involvement in 63 per cent of the patients, while similar symptoms for five to ten years increased the incidence to 75 per cent.

Repeated exacerbations of acute cholecystitis without jaundice increased the incidence of hepatic disease from 33 per cent at the end of one week to 50 per cent at two months and 66.6 per cent at three years (table 1).

Although 36.7 per cent of the 49 patients with quiescent disease of the gallbladder had a positive reaction to the colloidal gold test, the highest incidence of hepatic involvement occurred in the patients with the shortest duration of symptoms. In contrast to the groups with jaundice or infection, these patients showed a decrease in the incidence of hepatic damage as the period of quiescent disease of the gallbladder increased. The reaction to the colloidal gold test was positive in 11 of the 18 patients (61.1 per cent) with a history of six to twelve months' duration but indicated hepatic disease in only 4 of the 16 patients (25 per cent) whose history was of two to five years' duration and in 3 of the 15 patients (20 per cent) whose history extended over five years.

There appears to be a correlation between the bacterial flora of the gallbladder, the pathologic changes in the gallbladder and the incidence of disease of the liver as detected by the colloidal gold test (table 2). The gallbladder and bile of 22 patients with disease of the gallbladder were cultured. Growth was obtained in 14 of 22 instances. This consisted of Bacillus coli, which was the most prevalent organism, Pneumococcus type III, Streptococcus haemolyticus, Streptococcus viridans, Staphylococcus albus, Pseudomonas pyocyanea, Bacillus typhosus, Bacillus welchii and diphtheroids.

The reaction to the colloidal gold test was positive in 7 of the 14 patients (50 per cent) whose cultures were positive, in contrast to 2 of the 8 patients (25 per cent) whose gallbladder or bile yielded no bacteria. It is interesting to observe that the more virulent pathogenic organisms were isolated from the 7 patients with a positive reaction to the colloidal gold test, while such bacteria as Str. viridans, Staph. albus and diphtheroids were cultured from the biliary tracts of the 7 patients with no evidence of disease of the liver. Moreover, the pathologic changes in the gallbladder, both gross and microscopic, were more severe and extensive in the 7 patients with both a positive reaction to the colloidal gold test and virulent pathogenic organisms than in the 7 patients with a negative reaction to the colloidal gold test and less virulent bacteria (table 3).

COMMENT

The injurious effect on the liver of recurrent jaundice and infection of the gallbladder is readily demonstrable in table 1. Although the incidence of a positive reaction to the colloidal gold test was highest in the group of patients with both jaundice and infection (58.8 per cent), hepatic damage was equally prevalent in the patients with jaundice alone (52.5 per cent) or with infection of the gallbladder without jaundice (53.3 per cent). The danger of delaying surgical intervention too long is emphasized by the fact that the increase in the incidence of hepatic damage parallels the duration of the disease. Repeated insults to the liver from recurrent jaundice, infection of the gallbladder or both increased the incidence of disease of the liver to 75 per cent, 66.6 per cent and 100 per cent, respectively, as the duration of the disease was prolonged.

Jaundice and infection together appear to cause hepatic damage more rapidly than jaundice or infection alone, a pronounced increase in the incidence of hepatic disease occurring within a few weeks. Severe infection within the gallbladder likewise produces rapid hepatic damage, as seen in patient T. S. (table 3, patient 9), who complained of recurrent chills and fever of one month's duration. The reaction to the colloidal gold test was positive, and empyema of the gallbladder with gallstones was found at operation. Four similar instances of empyema of the gallbladder were observed. The patients all showed a positive reaction to the colloidal gold test.

The incidence of hepatic damage was considerably lower (36.7 per cent) in the 49 patients with gallstones and quiescent disease of the gallbladder without jaundice or clinical evidence of infection of the gallbladder. Although an infection of the gallbladder is always present in patients with gallstones, the process in patients without clinical evidence of infection is milder, and the pathologic changes are much less marked, than those observed in patients who manifest such evidence of infection (fever or leukocytosis) or jaundice. The highest incidence of disease of the liver (61.1 per cent) occurs during the more acute stages of the disease in these patients. The infection within the gallbladder then becomes quiescent and apparently mild, and as the period of inactivity increases the regenerative power of the liver is adequate to reduce the incidence of hepatic disease to about 20 per cent in the absence of any recurrent acute infection or jaundice.

The mild pathologic changes observed characteristically on microscopic examination of the gallbladders of patients with quiescent disease of the gallbladder of several years' duration were illustrated in 3 patients with vague abdominal distress and pain in the right upper quadrant of ten to twenty years' duration (table 3, patients 8, 13 and 14). Sterile cultures of the bile and gallbladder and negative reactions to the colloidal gold test were observed. At operation gallstones were found and the liver appeared normal.

Recurrent distress of the gallbladder of short duration without jaundice, fever or leukocytosis is associated with more acute changes within the gallbladder and a higher incidence of hepatic disease. An example of this was seen in patient L. H. (table 3, patient 15), who complained of recurrent mild colic of the gallbladder of nine months' duration. There was no evidence of jaundice, fever or leukocytosis. Gallstones were found at operation, and microscopic study of the gallbladder revealed an extensive round cell infiltration, hemorrhages and erosions. Str. viridans was cultured from the bile, and the reaction to the colloidal gold test was positive.

Recurrent infection of the biliary tract and jaundice of sufficient duration may result in cirrhosis of the liver. This was observed in 3 patients (table 3, patients 1, 2 and 6) with gallstones and recurrent fever, chills and jaundice of six to ten years' duration. The reaction to the colloidal gold test was strongly positive in all 3 patients, and microscopic studies of the liver revealed an extensive biliary cirrhosis in 2 (patients 1 and 6) and an early fibrosis with fatty infiltration in the third (patient 2). Severe inflammatory changes were observed in the gallbladders of all 3. It is interesting to observe that Str. haemolyticus was cultured from the gallbladders of 2 of the 3 patients and B. coli, Ps. pyocyanea and Str. viridans from that of the third. Other organisms found were type III pneumococcus and Staph. aureus.

The rapidity with which hepatic damage may be produced was demonstrated in a patient with mild diabetes (table 3, patient 3) who had colic of the gallbladder with jaundice and fever for ten days. The reaction to the colloidal gold test was positive ten days after the onset of symptoms. Two months later the gallbladder was removed; the reaction to the colloidal gold test had been positive repeatedly

during these two months. Gangrenous cholecystitis was found at operation, and a biopsy of the liver revealed marked fatty infiltration, round cell infiltration and vacuolation of the liver cells.

Carcinoma of the gallbladder is another complication of gallstones to be considered in the management of disease of the gallbladder. Adenocarcinoma of the gallbladder was found in 2 patients (table 3, patients 11 and 12) with cholelithiasis, in 1 of whom (patient 11) the tumor had invaded the liver. The reaction to the colloidal gold test was positive in this patient and negative in the one in whom no metastases to the liver were observed (patient 12). One patient with cholesterosis of the liver (patient 10) also had a positive reaction to the colloidal gold test.

Ravdin,[19] Portis [20] and others have emphasized the importance of evaluating hepatic insufficiency in the management of patients with disease of the gallbladder. The newer and more sensitive methods of detecting early disease of the liver should prove an additional guide in the preoperative and postoperative care of patients with disease of the biliary tract.

SUMMARY AND CONCLUSIONS

The colloidal gold test of hepatic function was performed on 100 patients with proved disease of the gallbladder. A positive reaction, indicating hepatic disease, was found in 46 per cent.

The incidence of disease of the liver was highest in the patients with jaundice and infection (58.8 per cent) and lowest in the patients with quiescent disease of the gallbladder (36.7 per cent) who presented no history or evidence of fever or jaundice.

The incidence of disease of the liver increased with the duration of infection of the gallbladder or jaundice but decreased with time in the group with quiescent disease of the gallbladder.

A correlation was noted between the bacterial flora of the gallbladder, the pathologic changes in the gallbladder and the incidence of hepatic disease.

Cirrhosis of the liver was found in 3 and carcinoma of the gallbladder in 2 of the 100 patients studied.

The importance of detecting early hepatic damage in the management of disease of the gallbladder was discussed.

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INFLUENCE OF THIAMINE ON INDUCED HYPERTHYROIDISM

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A study of the effects of thiamine on hypermetabolism induced by administration of desiccated thyroid gland was suggested by several observations. We noted that the administration of desiccated thyroid to depressed psychotic patients was associated with tachycardia, restlessness and apprehension of a degree which necessitated discontinuance of medication. Other patients, however, who previously had been given thiamine hydrochloride, tolerated the administration of desiccated thyroid well. They were less apprehensive and agitated, although the increase in the metabolic rate and in the cardiac rate were as great as in the previous group of patients.

Administration of small doses of desiccated thyroid to patients with a low basal metabolic rate often is attended by rapid action of the heart and complaints of nervousness and digestive disturbances. An increase in the basal metabolic rate could be accomplished in such patients with fewer complaints if adequate amounts of thiamine were given prior to the administration of desiccated thyroid.

In studies of induced deficiency of thiamine [1] the basal metabolic rates were found to be lowered in an irregular manner after several months of restriction of thiamine; they were lowered rarely when the deprivation of thiamine was severe and of short duration but more frequently when the deprivation was moderate and prolonged. In some subjects anemia developed, and it was thought that this effect of thiamine deprivation might account for the low metabolic rate. However, in other subjects anemia did not develop during the period of thiamine restriction, and in these the metabolic rates were equally low. The ultimate cause of the decrease of the basal metabolic rate of every subject was deprivation of thiamine, but the mechanism through which the deficiency of thiamine operated to produce the low metabolic rate was not clear. In every case administration of thiamine was associated with a return of the basal metabolic rate to normal, but the time of recovery of individual subjects was variable; weeks or months, even with vigorous treatment with thiamine, were sometimes required. Recovery of the rate of metabolic exchange to normal indicated that this adverse effect of deprivation of thiamine on the organism was slowly reversible. It generally is believed that a high rate of metabolism is associated with a high requirement for

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thiamine and, conversely, a low rate of metabolism with a low requirement for thiamine. Regardless of the mechanism involved, the lowering of the basal metabolic rate in thiamine deficiency would be protective and spare the tissue stores of cocarboxylase. In a study not yet reported, a low basal metabolic rate was not observed among 4 subjects who received 0.7 mg. of riboflavin per day (0.35 mg. per thousand calories) for two hundred and sixty-nine days.

It may be assumed that the initial decrease of the metabolic rate in thiamine deficiency is produced by suppression of secretory activity of the thyroid gland or that the hormone of the thyroid is less effective in physiologic processes if there is a deficiency of thiamine. The latter consideration would have a particu-

TABLE 1.—*Composition of Basal Diet* *

Food	State of Preparation	Menu 1, Gm.	Menu 2, Gm.	Menu 3, Gm.
Bread	Special recipe	230	230	230
Butter	As purchased	45	45	45
Cream, 35 per cent	As purchased	75	75	75
Beef, lean	Roasted	100	100	75
Sucrose	As purchased	50	50	50
Cake	Special recipe	50	50	50
Potato, Irish	Roasted	75	75	100
Rice, polished, dry	Boiled	25	25	25
Flour	Plain white	10	10	10
Jelly	As purchased	20	20	20
Puffed rice	Commercial (unfortified)	15	..	..
Carrots	Canned	75	..	..
Lettuce	Fresh	30	..	..
Pineapple	Canned	80	80	..
Gelatin, 20 per cent solution	Special recipe	100	..	100
Tomato	Canned	75	..	..
Apricots, dried, sulfured	Cooked	30	..	..
Farina, dry	Cooked	..	15	15
Apple sauce	Cooked	..	100	100
Lemon juice	Fresh	..	20	20
Celery	Fresh	..	30	30
Corn	Canned	..	50	..
Cottage cheese	Washed, skimmed	..	35	35
Beets	Canned	..	..	50
Composition of standard diet † :				
Carbohydrate			327 Gm.	
Protein			67 Gm.	
Fat			75 Gm.	
Calories			2,260	
Thiamine			0.43 to 0.48 mg. (0.21 mg. per 1,000 calories)	

* Each menu was repeated every third day. Vitamin supplements were given as described in the text.

† The content of carbohydrate, protein and fat was calculated from the data of Chatfield and Adams (Chatfield, C., and Adams, G.: Proximate Composition of American Food Materials, no. 549, United States Department of Agriculture, June, 1940). The content of thiamine was determined by the thiochrome method of Hennessy.[2]

lar bearing if the thyroid hormone affects primarily the mobilization of materials for oxidation and other enzyme systems have the role of oxidation of the mobilized intermediary metabolites.

In the study herewith reported, the influence of any decrease of activity of the thyroid gland during the restriction of thiamine was obviated by administration of desiccated thyroid at a level somewhat higher than the normal requirement. Therefore, we were able to study the effectiveness of the thyroid hormone in maintaining the metabolic rate during deprivation of thiamine. Volunteer subjects were used.

METHODS OF STUDY

The subjects were studied in the nutrition division and were provided with an ample diet and supplements of 2 mg. of thiamine hydrochloride, 2 mg. of riboflavin, 4 mg. of pyridoxine hydrochloride, 10 mg. of calcium pantothenate, 40 mg. of nicotinic acid amide, 160 mg. of

ascorbic acid and 0.2 Gm. of halibut liver oil fortified with irradiated ergosterol (providing 10,000 U. S. P. units of vitamin A and 4,000 U. S. P. units of vitamin D) per day for thirty days to assure a good nutritional status. During the period of preliminary observation the subjects were accustomed to procedures and routines and, especially tests of the basal metabolism. After the period of preliminary observation 2 women (subject 1, aged 47, 172 cm. tall; subject 2, aged 25, 158 cm. tall) were selected for further study. These did not have any signs of nutritional disease or physical defects and were able and willing to cooperate.

The diet, given in table 1, was constructed of foods which commonly appear on American tables and contained 0.22 mg. of thiamine per thousand calories. This diet was used through the entire period of study. It was analyzed for content of thiamine by the thiochrome method of Hennessy.[2] The caloric intake was adjusted to the requirement of the subject by giving fractions or multiples of the standard servings of the basal diet. Thus the ratio of thiamine to calories was maintained nearly constant.

In the period of study (Oct. 5, 1941 to June 1, 1942) the diet was supplemented per day with 4 mg. of riboflavin, 8 mg. of pyridoxine hydrochloride, 20 mg. of calcium pantothenate, 80 mg. of nicotinic acid amide, 160 mg. of ascorbic acid, 0.4 Gm. of halibut liver oil fortified with irradiated ergosterol (providing 20,000 U. S. P. units of vitamin A and 8,000 U. S. P. units of vitamin D), 0.25 Gm. of choline chloride, 0.2 Gm. of ferrous sulfate, 0.6 Gm. of tribasic calcium phosphate and 5 minims (0.3 cc.) of compound solution of iodine U. S. P. The diet was supplemented with thiamine hydrochloride only in the first two and last two periods of study, in the amounts indicated in tables 2 and 3. In the third period deprivation of thiamine represented, so far as could be judged, the only dietary restriction.

In the period of preliminary observation, at intervals during the period of restriction of thiamine and again during the subsequent periods of administration of thiamine, determinations of the basal metabolic rate; determinations of the calcium, phosphorus and proteins in the serum; determinations of the lipids in the plasma; electrocardiograms, and blood counts were made. The pyruvic acid,[3] lactic acid [4] and dextrose [5] in the blood were determined when the subject was at rest in bed and after administration of dextrose orally and intravenously. Both oral and intravenous tests for dextrose tolerance were performed with the subject in the postabsorptive state and at rest in bed. For the oral test 50 Gm. of dextrose in 250 cc. of solution was given and repeated thirty minutes later (Exton-Rose dextrose tolerance test [6]). Samples of blood were taken for analysis just before administration of the first dose of dextrose and again at thirty, sixty and ninety minutes after administration of this dose. The values at sixty and ninety minutes are the most significant. Data on the determinations at sixty minutes are contained in tables 2 and 3. For the intravenous test 0.4 Gm. of dextrose (0.8 cc. of a 50 per cent solution of dextrose) per kilogram of body weight was administered in three minutes. The concentrations of pyruvic acid, lactic acid and dextrose in the blood were determined before administration of dextrose and at thirty, sixty and one hundred and twenty minutes after injection. The values at thirty minutes are the most significant. The results of the intravenous test were comparable to those of the oral test and are not included in the presentation of data. Data on the pyruvic acid, lactic acid and dextrose in the blood after administration of dextrose, dextrose plus insulin and insulin alone are contained in table 4.

An exercise test was standardized for each subject. It consisted of a unit of work completed in exactly two minutes. Samples of blood for analysis of the content of pyruvic acid and lactic acid were taken just before exercise, the subject being at rest in bed and in the postabsorptive state, and at five, thirty and sixty minutes after conclusion of the exercise. The results are contained in table 5.

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TABLE 2.—*Observations on Subject 1*

Duration of Period, Days	Diet: Carbohydrate, Gm.	Diet: Protein, Gm.	Diet: Fat, Gm.	Diet: Calories	Diet: Thiamine, Micrograms	Diet: Thiamine Supplement, Micrograms	Excretion of Thiamine, Micrograms: In 24 Hr.	Excretion of Thiamine, Micrograms: In 4 Hr. After Test Dose †	Body Weight, Kg.	Basal Blood Pressure, Mm. Hg: Systolic	Basal Blood Pressure, Mm. Hg: Diastolic	Basal Pulse Rate	Basal Metabolic Rate: Maximum, per Cent	Basal Metabolic Rate: Minimum, per Cent	Biochemical Status *: Pyruvic Acid, Mg. per 100 Cc.	Biochemical Status *: Lactic Acid, Mg. per 100 Cc.	Biochemical Status *: Dextrose, Mg. per 100 Cc.
Period of Administration of Thiamine																	
13	321	65	90	2,350	602	4,000	...	430	63.6	118	60	78	−13	−13	1.3	8.6	154
Period of Administration of Thiamine and Thyroid ‡																	
13	318	65	87	2,315	482	4,000	...	463	63.0	114	76	91	+15	+ 7	1.9	12.5	162
22	307	67	87	2,279	479	9,500	...	...	62.2	118	60	105	+23	+21	1.8	16.1	185
Period of Restriction of Thiamine and Administration of Thyroid ‡																	
15	319	68	86	2,322	497	.....	80	...	62.0	110	64	88	+14	+12	...	....	...
32	331	67	85	2,357	458	.....	...	...	62.0	120	80	87	+13	+13	2.0	16.3	186
46	330	67	77	2,281	497	.....	...	...	61.8	116	74	86	+17	+14	...	....	...
61	328	67	72	2,228	475	.....	56	...	61.4	118	72	98	+17	+15	2.7	18.7	180
74	326	66	71	2,207	449	.....	...	...	60.9	112	70	90	− 6	− 8	...	....	...
88	327	65	75	2,243	430	.....	27	...	60.4	114	70	81	+12	+11	...	....	...
103	323	69	73	2,225	454	.....	...	...	60.0	101	66	98	+ 7	+ 5	2.4	19.6	158
117	323	65	75	2,227	439	.....	7	66	61.2	114	72	90	+10	+10	3.2	20.9	134
136	316	65	75	2,199	456	.....	7	56	59.7	104	60	84	+12	+12	3.7	26.5	162
Period of Administration of Thyroid ‡ and Increasing Amounts of Thiamine																	
17	326	66	77	2,261	455	300	26	156	58.6	106	62	87	+11	+ 8	2.4	16.2	172
33	342	67	79	2,347	482	600	45	125	57.8	104	54	80	+ 8	+ 7	2.3	15.9	187
47	283	55	70	1,982	422	900	272	266	57.1	122	70	89	+22	+21	2.3	16.8	155
61	311	62	75	2,167	447	1,200	415	284	56.0	122	80	99	+19	+15	1.8	10.4	176
81	314	65	76	2,200	453	19,000	...	...	59.0	126	82	93	+29	+28	2.6	23.5	155
Period of Administration of Thiamine																	
13	320	66	74	2,210	460	4,000	...	...	58.6	130	72	80	+11	+ 6	1.6	12.5	168
26	340	70	70	2,270	466	4,000	...	...	59.0	128	75	74	+ 6	0	1.3	10.6	166

* Sixty minutes after the first dose of dextrose given orally.
† One milligram of thiamine hydrochloride given subcutaneously.
‡ Sixth-tenths gram of desiccated thyroid per day.

TABLE 3.—*Observations on Subject 2*

Duration of Period, Days	Diet: Carbohydrate, Gm.	Diet: Protein, Gm.	Diet: Fat, Gm.	Diet: Calories	Diet: Thiamine, Micrograms	Diet: Thiamine Supplement, Micrograms	Excretion of Thiamine, Micrograms: In 24 Hr.	Excretion of Thiamine, Micrograms: In 4 Hr. After Test Dose †	Body Weight, Kg.	Basal Blood Pressure, Mm. Hg: Systolic	Basal Blood Pressure, Mm. Hg: Diastolic	Basal Pulse Rate	Basal Metabolic Rate: Maximum, per Cent	Basal Metabolic Rate: Minimum, per Cent	Biochemical Status *: Pyruvic Acid, Mg. per 100 Cc.	Biochemical Status *: Lactic Acid, Mg. per 100 Cc.	Biochemical Status *: Dextrose, Mg. per 100 Cc.
Period of Administration of Thiamine																	
6	340	72	81	2,377	451	4,000	...	463	56.9	108	58	72	+ 8	+ 4	1.3	8.6	148
Period of Administration of Thiamine and Thyroid ‡																	
6	320	66	81	2,273	448	4,000	...	...	57.0	118	66	110	+17	+12	...	....	...
22	315	70	85	2,305	462	9,500	...	484	57.3	118	50	90	+22	+20	2.10	15.8	168
Period of Administration of Thyroid ‡; Restriction of Thiamine																	
15	308	68	86	2,278	503	.....	88	...	57.4	125	54	87	+16	+16	...	....	...
32	312	67	84	2,272	499	.....	...	...	57.5	124	50	90	+20	+20	2.12	16.4	152
46	324	67	73	2,221	490	.....	....	...	57.2	130	58	102	+22	+18	...	....	...
61	336	68	71	2,255	464	.....	47	...	55.6	130	60	114	+20	+20	2.00	15.2	172
74	330	66	74	2,340	449	.....	...	...	55.5	132	70	96	+11	+11	...	....	...
88	333	66	74	2,262	423	.....	23	...	56.0	116	54	80	+19	+18	...	....	...
103	320	68	74	2,218	453	.....	...	...	55.0	118	52	83	+27	+25	...	....	...
117	326	64	75	2,235	450	.....	13	35	54.6	124	58	73	+16	+14	2.30	20.6	157
136	337	69	79	2,335	473	.....	7	48	54.6	128	50	89	+17	+16	3.50	28.4	167
Period of Administration of Thyroid ‡ and Increasing Amounts of Thiamine																	
17	345	67	78	2,350	467	300	57	130	54.2	122	68	79	+15	+14	2.30	19.1	166
33	332	67	79	2,307	466	600	172	200	53.3	148	50	78	+22	+20	2.00	15.4	204
47	346	67	78	2,354	486	900	248	323	53.6	112	58	93	+34	+33	1.90	15.1	159
61	321	65	77	2,237	453	1,200	735	294	52.6	118	64	72	+33	+32	2.20	16.3	131
81	340	67	77	2,321	488	19,000	...	...	52.4	128	68	76	+34	+28	2.00	16.8	146
Period of Administration of Thiamine																	
13	340	65	76	2,304	470	4,000	...	...	50.4	118	68	80	+ 2	0	1.60	13.4	146
26	320	68	75	2,227	465	4,000	...	...	53.0	122	74	78	0	— 5	1.30	10.2	152

* Sixty minutes after the first dose of dextrose given orally.
† One milligram of thiamine hydrochloride given subcutaneously.
‡ Five-tenths gram of desiccated thyroid per day.

Physical and neurologic examinations were made not less frequently than once each month. The urine was analyzed periodically for content of thiamine by the method of Hennessy.[2] Determinations of the twenty-four hour excretion served as a check on the intake of thiamine. At the end of the period of restriction of thiamine 1 mg. of thiamine hydrochloride was given subcutaneously and the excretion determined for the ensuing four hours, the subject being maintained in the postabsorptive state. The excretion of the test dose of thiamine indicated in some measure the stores of thiamine in the tissues. The value of the test dose procedure for estimation of these stores has been discussed in another paper,[7] and additional data were provided by a study, not yet reported, on the thiamine requirements of man. It suffices to state here that an excretion of 200 micrograms or more within four hours after administration of 1 mg. of thiamine indicates satisfactory stores of thiamine and that an excretion of less than 100 micrograms indicates a considerable depletion of these stores.

Basal metabolic rates were determined with a specially constructed Benedict-Roth type apparatus. The rate was determined for two ten minute periods on the day of the test. The large capacity of the oxygen reservoir of the machine, an excursion of 1 cm. of the drum representing 503.7 cc. of oxygen, made for accuracy in the determination of the slopes of the curves. For convenience of presentation the basal metabolic rates in terms of calories

TABLE 4.—*A Comparison of the Concentrations of Pyruvic Acid, Lactic Acid and Dextrose in the Blood of Subject 1 After Administration of Dextrose, Dextrose and Insulin or Insulin Alone (Preliminary Period) with Those After Administration of Thyroid and Thiamine* *

Procedure (Administration)	Excretion of Thiamine in 4 Hrs. After Test Dose, Micrograms	Basal Metabolic Rate on Day of Test, per Cent	Time of Analysis of Blood: Minutes After Administration of Insulin †					Minutes After Administration of Dextrose †										
			0	15	45	75	105	0	15	45	75	105	0	15	45	75	105	
			x	0	30	60	90	x	0	30	60	90	x	0	30	60	90	
			Pyruvic Acid, Mg. per 100 Cc.					Lactic Acid, Mg. per 100 Cc.					Dextrose, Mg. per 100 Cc.					
Before Administration of Thyroid																		
Dextrose	...	—10	...	1.1	1.2	1.5	1.5	...	8.2	11.6	14.9	15.3	...	90	152	144	107	
Dextrose plus insulin	440	— 9	1.1	1.3	1.8	1.9	2.3	3.5	6.8	10.2	14.8	18.6	99	105	82	89	94	
Insulin	...	— 8	1.1	1.3	1.7	2.0	2.2	2.4	6.0	9.4	13.9	17.2	102	62	38	49	50	
After Administration of Thyroid																		
Dextrose	...	+21	...	1.1	1.8	2.5	2.9	...	6.3	14.2	22.6	27.4	...	98	140	178	118	
Dextrose plus insulin	457	+23	1.2	1.5	2.4	2.4	2.1	6.0	9.8	22.2	22.5	17.8	92	74	60	85	102	
Insulin	...	+25	1.5	1.9	2.7	2.8	2.8	7.0	15.4	26.6	34.2	33.5	89	61	41	44	47	

* The intake of desiccated thyroid was 0.6 Gm. per day; the intake of thiamine hydrochloride was 4 500 micrograms per day at the time of the test in both periods.

† Insulin was given intravenously; in the insulin-dextrose test 40 units of regular insulin was given fifteen minutes before the first dose of dextrose. Dextrose was given orally, 50 Gm. at zero time and another 50 Gm. thirty minutes later.

per square meter of body surface have been converted into percentage of normal by the standards of Boothby and Berkson (1935).[8]

The basal pulse rate for a period of two minutes and the basal blood pressure were determined before the subject arose each morning and were checked by a second observer.

Continuously throughout the period of administration of thyroid U. S. P., 0.6 Gm. (10 grains) per day was given to subject 1 and 0.5 Gm. (8 grains) to subject 2. The preparation was made up into uncoated tablets which contained 0.06 Gm. of desiccated thyroid per tablet. The daily dose was divided into two equal portions, and one portion was administered after each of two of the meals of the day. Frequent examination of the feces revealed no undigested tablets. Diarrhea was never observed, and disturbance of gastrointestinal motility was not detected in periodic estimations of the motility rate by roentgen examination after a meal of barium sulfate. The conditions of the study were strictly maintained.

7. Mason, H. L., and Williams, R. D.: The Urinary Excretion of Thiamine as an Index of the Nutritional Level: Assessment of the Value of a Test Dose, J. Clin. Investigation **21**:247-255 (March) 1942.

8. Boothby, W. M.; Berkson, J., and Dunn, H. L.: Studies on the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism, with a Nomogram for Clinical Application, Am. J. Physiol. **116**:468-484 (July) 1936.

TABLE 5.—*Data on Pyruvic Acid and Lactic Acid in the Blood After Administration of Dextrose Orally and After Exercise: Effects of Treatment with Thiamine Hydrochloride*

Duration of Intake Level, Days	Intake of Thiamine, Micrograms	Excretion of Thiamine, Micrograms: In 24 Hr.	Excretion of Thiamine, Micrograms: In 4 Hr. After Test Dose	Minimal Basal Metabolic Rate, per Cent	Response to Dextrose *: Pyruvic Acid, Mg. per 100 Cc.: Basal State	30 Min.	60 Min.	90 Min.	Response to Dextrose *: Lactic Acid, Mg. per 100 Cc.: Basal State	30 Min.	60 Min.	90 Min.	Response to Exercise †: Pyruvic Acid, Mg. per 100 Cc.: Basal State	5 Min.	30 Min.	60 Min.	Response to Exercise †: Lactic Acid, Mg. per 100 Cc.: Basal State	30 Min.	60 Min.	90 Min.
Subject 1																					
136‡	450	7	56	+10	1.1	2.6	3.7	3.1	3.4	13.9	26.5	24.7	1.2	5.0	2.8	1.5	4.4	41.4	20.4	8.6
17	750	26	156	+11	1.0	1.7	2.4	2.4	3.8	7.6	16.2	18.2	1.3	4.3	2.9	2.1	4.7	44.8	21.5	12.1
16	1,050	45	125	+ 8	...	...	2.3	1.9	...	....	16.8	13.0	1.1	4.6	3.4	2.6	5.1	50.3	30.6	15.2
14	19,450	...	...	+29	...	...	1.9	2.1	...	....	16.0	21.3	1.0	4.7	3.8	2.9	5.0	58.4	36.2	18.6
Subject 2																					
136‡	450	7	48	+17	1.1	2.9	3.5	3.1	3.7	16.0	28.4	27.9	1.0	3.3	2.3	1.6	3.8	38.8	15.2	8.0
17	750	57	130	+15	1.0	1.8	2.3	2.1	4.3	10.5	19.1	18.6	1.1	4.1	3.0	1.6	4.2	47.7	25.8	10.0
16	1,050	172	200	+22	1.1	1.5	2.0	2.0	4.7	7.0	15.4	17.0	1.0	4.5	3.2	1.8	4.9	63.0	34.0	14.7
14	19,450	...	...	+34	...	...	1.9	1.9	...	....	15.1	18.3	1.1	4.5	3.6	2.0	4.5	70.0	38.4	18.1
Control Subject A																					
100	1 000	800	336	— 2	1.0	1.2	1.4	1.2	6.4	7.3	9.5	8.5	1.1	3.9	2.6	1.5	5.4	47.1	23.9	11.4
Control Subject B																					
100	1,600	895	355	—11	0.8	1.1	1.2	1.3	3.8	6.0	10.3	12.2	1.0	3.6	2.9	2.1	4.5	41.4	36.4	20.3

* Fifty grams of dextrose was given at zero time and 50 Gm. thirty minutes later.
† The test was standardized for the individual subject: one unit of work in exactly two minutes. Samples of blood were taken at intervals after discontinuance of exercise.
‡ End of the period of deprivation of thiamine.

OBSERVATIONS IN VARIOUS PERIODS OF THE STUDY

Period of Administration of Thiamine (Preliminary Period).—In this period the first of the series of periodic examinations was made. Data on the pyruvic acid, lactic acid and dextrose in the blood after administration of dextrose are contained in tables 2, 3 and 5. The data of this period are typical of those from studies of many other subjects, and therefore they serve as "normal" data for reference in subsequent determinations.

Period of Administration of Desiccated Thyroid and Thiamine.—This period, of twenty-two days, began October 5 and ended October 26. Administration of the relatively large doses of desiccated thyroid was associated with an increase of the basal metabolic and the cardiac rate and some degree of hyperactivity, but there were no subjective symptoms which caused complaints. The concentrations of pyruvic acid and lactic acid in the blood were normal when the subject was at rest in bed. However, they were abnormally high after exercise and after administration of dextrose. Data on pyruvic acid and lactic acid are contained in tables 2, 3 and 4. Electrocardiographic abnormalities other than sinus tachycardia and arrhythmia were not observed. The basal metabolic rates at the end of the period were approximately + 20 per cent.

Period of Administration of Desiccated Thyroid and Restriction of Thiamine.—This period, of one hundred and thirty-six days, began Oct. 27, 1941 and ended March 11, 1942. Discontinuance of the administration of thiamine hydrochloride was associated with anorexia, fatigue and nervousness for a few days, but readjustment occurred to the lower intake of thiamine, for complaints were not again voiced until about the seventieth day. Both subjects then complained of loss of appetite, fatigue, nervousness, numbness and tingling of the feet and legs and aching of the muscles of the calves. There was some decrease of ability to rise from the squatting position or to mount a chair. The achilles tendon and patellar reflexes were moderately hyperactive. Defects of the sensory nerve pathways were not observed. The cardiac rate was not rapid (70 to 90 beats per minute) when the subjects had been at rest in bed, but it was rapid (100 to 130 beats per minute) when there had been even moderate exertion. In thiamine deficiency, bradycardia during rest in bed and tachycardia after exertion have been regularly observed.[1] The blood pressure was somewhat affected; the diastolic pressure tended to fall more than the systolic. The heart sounds were fainter, and the pulse at the wrist was weaker than it had been at previous examinations. The chief features in the electrocardiograms were evidence of sinus tachycardia and arrhythmia with some decrease in the amplitude of all complexes. The basal metabolic rates were decreased irregularly at levels as low as — 7 to + 11 per cent.

After one hundred and thirty-six days of restriction of thiamine, anorexia, weakness and soreness of the muscles of the legs were outstanding complaints. Nausea was becoming more frequent; maintenance of intake of food and of activity required vigorous persuasion. Weakness of the muscles of the calves of the legs made it extremely difficult for subject 1 to rise from the squatting position or to mount a chair, and subject 2 could not rise from the squatting position. The achilles tendon and patellar reflexes of subject 1 had disappeared, and, while the right patellar reflex of subject 2 could be obtained, the left patellar and both achilles tendon reflexes were absent. Acuity of perception of stimuli, such as the touch of a cotton wisp, a pin prick and application of warm and cool tubes to the thighs and legs, did not appear impaired, although subject 1 occasionally responded inaccurately. A definite defect in the sense of position of joints or

of perception of vibrations of the tuning fork (128 vibrations per second) was not observed. The plantar reflexes (Babinski) were not obtained. In a study not yet reported severe neurologic defects were caused by isolated deficiency of thiamine.

The systolic blood pressure of subject 2 had increased and that of subject 1 decreased. The diastolic pressure was approximately 50 mm. of mercury. The pulse had a slapping quality at the wrist which was out of proportion to the pulse pressure observed. The electrocardiogram of subject 1 revealed a sinus tachycardia, slurring of the QRS complex in leads II and III, a tendency to left axis deviation, inversion of the T wave in lead III and inversion of the P wave in lead III. The T wave of lead IV R was positive; in lead CR_2 the T wave was diphasic and the R wave diminished. The outstanding features of the electrocardiograms of subject 2 were sinus arrhythmia, slurring of the QRS complex in lead II and notching of the QRS complex in lead III. In lead III both the T wave and the P wave were diphasic. In lead IV R the T wave was positive, the Q wave small and the ST segment elevated. In lead CR_2 the T wave was positive.

The basal metabolic rate of each subject after one hundred and thirty-six days of restriction of thiamine and administration of desiccated thyroid was somewhat higher than it had been on the seventy-fourth day. The concentrations of pyruvic acid and lactic acid in the serum after administration of dextrose were considerably increased above the initial value, which indicated that the high values for pyruvic acid incident to a deficiency of thiamine were superimposed on already high values incident to the administration of desiccated thyroid.

The progressive nature of the neurologic defects and the other signs and symptoms of a deficiency of thiamine necessitated discontinuance of its restriction, and therefore thiamine was administered in increasing amounts beginning March 12, 1942.

Period of Administration of Thyroid and of Increasing Amounts of Thiamine.—Beginning March 12, 1942, thiamine hydrochloride was provided in increasing amounts so that data might be obtained on the requirement for thiamine in conditions of induced hypermetabolism. The initial supplement of thiamine hydrochloride was 300 micrograms per day. The daily dose was increased by 300 micrograms approximately every two weeks. A satisfactory excretion of thiamine (more than 200 micrograms per twenty-four hours or more than 200 micrograms per four hours after administration of 1 mg. of thiamine hydrochloride subcutaneously) was not obtained until the intake of thiamine hydrochloride was about 0.6 mg. per thousand calories. This represents a somewhat higher minimal intake than was required by subjects with normal basal metabolic rates (0.45 mg. per thousand calories). The minimal intake of 0.6 mg. per thousand calories cannot be set with certainty because the subjects began the period of increasing intake of thiamine with depleted stores of thiamine and because the only objective criterion for adequacy of intake was excretion of thiamine; other criteria which we have used to assess the status of thiamine nutrition were not applicable in the state of induced hypermetabolism. These data might tentatively be interpreted, however, as evidence that the rate of metabolic exchange as well as the total exchange of energy or materials influences the requirement for thiamine.

When the larger doses of thiamine hydrochloride (more than 0.6 mg. per thousand calories) were administered, the basal metabolic rate rose to levels of + 21 to + 28 per cent for subject 1 and of + 28 to + 34 per cent for subject 2. The levels of pyruvic acid and lactic acid in the blood after administration

of dextrose fell only slightly in this entire period, and after exercise these levels were even higher than during the period of deficiency of thiamine (table 5).

Treatment with small doses of thiamine produced numerous complaints of anorexia, weakness and nervousness. Although the intake of food was approximately the same as in previous periods, the subjects lost weight rapidly. Further loss of weight was prevented for subject 2 and a gain secured for subject 1 when the intake of thiamine hydrochloride was raised to about 19.5 mg. per day. It is assumed that the sharp rise in the metabolic rate incident to administration of thiamine caused the complaints and loss of weight, an apparent paradoxic response to treatment.

Appetite and strength rapidly returned when the larger doses of thiamine were administered. Neurologic defects incident to deprivation of thiamine disappeared gradually from subject 2, but the achilles tendon reflexes of subject 1 were absent even after one hundred and twenty days of treatment.

Period of Administration of Thiamine Without Administration of Desiccated Thyroid.—When thyroid medication was discontinued, the basal metabolic rates fell to normal levels within two weeks. Normal values for pyruvic acid and lactic acid in the blood after administration of dextrose were obtained, this fact indicating that the abnormal values encountered during the period of administration of desiccated thyroid and thiamine were caused by an increased rate of metabolism and not by a deficiency of thiamine.

COMMENT

The data in tables 2 and 3 on the basal metabolic rates indicate that these were initially increased by administration of desiccated thyroid. The rates, which decreased irregularly during deprivation of thiamine, rose to consistently high levels when thiamine hydrochloride was again provided, no other change having been made in the regimen. These data seem to indicate that the thyroid hormone is less effective for the maintenance of metabolic processes during thiamine deficiency. In drawing this conclusion we assumed, however, that (1) administration of desiccated thyroid at a level somewhat higher than the normal requirement for the thyroid hormone reduces the activity of the thyroid gland to a minimum, and, therefore, a further reduction of secretory activity of the thyroid gland is not caused by the deficiency of thiamine, and (2) absorption of desiccated thyroid gland is not impaired during deprivation of thiamine. Evidence for or against the validity of these assumptions was not obtained.

The data provide additional evidence that the function of the thyroid hormone is primarily to mobilize metabolites for oxidation by enzyme systems of the organism.

The values for pyruvic acid and lactic acid in the blood after administration of dextrose (contained in tables 2, 3 and 4) indicate that the levels of these substances in the blood, and presumably in the tissues, were elevated during hypermetabolic activity induced by administration of desiccated thyroid. Elevated levels of intermediary metabolites in the blood and tissues might in themselves serve to exert a mass action effect which would produce a metabolic rate higher than normal. Data on subjects 1 and 2 for the period of deprivation of thiamine indicate that the levels of these substances rose in the state of thiamine deficiency and that the abnormal levels were corrected slightly when thiamine was administered and in full only when administration of desiccated thyroid was discontinued.

The data contained in table 5 illustrate an apparently paradoxic response to treatment with thiamine. At the end of the period of deprivation of thiamine, high values for pyruvic acid and lactic acid were encountered after administration of dextrose. These metabolites decreased with administration of thiamine approximately to the levels encountered in the second period of study (period of administration of desiccated thyroid with adequate thiamine). This indicates a cure of the metabolic defect caused by a deficiency of thiamine; however, at the end of the period of deprivation of thiamine the levels of pyruvic acid and lactic acid after a standardized exercise test were approximately the same (in a few instances higher and in others lower) as those for normal control subjects. After administration of thiamine these levels after exercise became considerably higher. This apparent increase in the rate of mobilization of metabolites was associated with the increase in metabolic rate which followed administration of thiamine; the administration of desiccated thyroid was held constant.

SUMMARY AND CONCLUSIONS

Two physically healthy women, maintained continuously on a basal diet providing only 0.22 mg. of thiamine per thousand calories but adequate in all other respects, received large doses of desiccated thyroid gland (subject 1, 0.6 Gm. per day, subject 2, 0.5 Gm.) for two hundred and forty-one days. Besides the periods of preliminary and subsequent observation the study was divided into three periods: Thiamine hydrochloride was liberally provided during the first period, of twenty-two days; it was restricted to 0.45 mg. per day during the second period, of one hundred and thirty-six days; it was provided in increasing amounts during the third period, of eighty-one days.

The basal metabolic rate of each subject rose to approximately + 25 per cent during the initial period of administration of thiamine and desiccated thyroid. It fell to — 8 per cent and + 11 per cent, respectively, during the period of restriction of thiamine, but rose to approximately + 25 and + 30 per cent, respectively, in the third period, when thiamine hydrochloride was again provided.

Throughout the period of administration of desiccated thyroid the concentrations of pyruvic acid and lactic acid in the blood after administration of dextrose were high, but they were higher during the period of restriction of thiamine.

The conclusion appears justified that the thyroid hormone is less effective in promoting the metabolic activity of the organism in a state of thiamine deficiency. The results of this study may be interpreted as additional evidence that the function of the thyroid hormone is primarily to mobilize metabolites for oxidation by enzyme systems of the organism and only indirectly to increase the rate of oxidative processes.

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ELECTROCARDIOGRAPHIC CRITERIA OF LEFT VENTRICULAR HYPERTROPHY

FACTORS DETERMINING THE EVOLUTION OF THE ELECTROCARDIOGRAPHIC PATTERNS IN HYPERTROPHY AND BUNDLE BRANCH BLOCK

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Soon after the advent of clinical electrocardiography it was recognized by Einthoven and others that characteristic deviations occur in association with hypertrophy of the cardiac chambers. Important contributions were made by several early investigators,[1] but for a long time interest in electrocardiography was focused chiefly on differentiation of the arrhythmias and the diagnosis of myocardial disease, with little emphasis on the clinical value of the electrocardiogram as a means of detecting cardiac hypertrophy.

While the association of characteristic electrocardiographic patterns with hypertrophy of the various cardiac chambers is well recognized, the mechanism of these changes remains a subject of some controversy, and specific criteria for the electrocardiographic diagnosis of hypertrophy have not been established.

The present investigation was actuated by the necessity of establishing specific electrocardiographic criteria of left ventricular hypertrophy in connection with a study on prognosis of hypertension.[2] It was felt, and the belief was subsequently confirmed, that prognosis of hypertension was dependent not solely on the level of the blood pressure but on the duration of the hypertension, as evidenced by the degree of left ventricular enlargement. In order to classify subjects into

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2. Daley, R. M.; Ungerleider, H. E., and Gubner, R. S.: Prognosis and Insurability of Hypertension with Particular Reference to the Electrocardiogram, Proc. A. Life Insur. M. Dir. America **28**:18, 1941.

groups with and without electrocardiographic evidence of left ventricular hypertrophy, so that an actuarial mortality study could be made, it was first necessary to ascertain precisely what electrocardiographic abnormalities could be considered indicative of left ventricular hypertrophy.

ELECTROCARDIOGRAPHIC CRITERIA OF LEFT VENTRICULAR HYPERTROPHY

It is generally appreciated that left axis deviation alone is of no significance as a sign of left ventricular hypertrophy, since it occurs in a large proportion of normal subjects. A study was therefore made to establish what electrocardiographic changes in association with left axis deviation could be considered indicative of hypertrophy.

The material for study comprised three groups of subjects: (1) 460 applicants for insurance with left axis deviation whose blood pressure was always below 140 systolic and 90 diastolic and for whom there was no record nor finding of any cardiac impairment; (2) 380 applicants with hypertension with left axis deviation whose blood pressure was always above 140 systolic and 90 diastolic, and

TABLE 1.—*Voltage of the Ventricular Complex in Left Ventricular Hypertrophy*

	95%		99%		99.9%	
Criterion	Of "Normal" Subjects Are Below This Point	Which is Exceeded by This Percentage of Hypertrophy	Of "Normal" Subjects Are Below This Point	Which is Exceeded by This Percentage of Hypertrophy	Of "Normal" Subjects Are Below This Point	Which is Exceeded by This Percentage of Hypertrophy
R_1	13.9 mm.	60.1	15.8 mm.	42.6	18.1 mm.	23.5
$R_3 + S_3$	22.1 mm.	67.0	25.4 mm.	51.9	29.1 mm.	34.7
Higher of R_1 and S_3	14.0 mm.	63.6	16.1 mm.	45.7	18.4 mm.	27.1
Higher of $(R_1 + S_1)$ and $(R_1 + S_3)$	15.6 mm.	62.6	17.7 mm.	46.0	20.2 mm.	27.4
$(R_1 + S_3)$ minus $(S_1 + R_3)$	19.2 mm.	65.1	22.5 mm.	50.0	26.1 mm.	33.6

(3) 100 subjects with advanced hypertensive heart disease with left axis deviation in whom it may be assumed that left ventricular hypertrophy was present.

Group 1 was taken as normal, and group 3 represented hypertrophy. Group 2, consisting of applicants with hypertension, may be regarded as a mixed group in which a certain proportion of subjects had hypertrophy while the remainder were normal.

A study was made of the voltage of the QRS complex and of changes in the ST segment and the T wave. In the consideration of voltage two questions were investigated: 1. What combination of measurements of the R and the S wave in lead I and lead III is the most efficient criterion for the separation of persons with normal hearts from those with hypertrophy of the left ventricle? 2. With this criterion determined what is the dividing line between normal and abnormal hearts?

Five combinations of the R and the S wave in the standard limb leads were investigated: (1) the amplitude of R_1; (2) the sum of the amplitude of R_1 and of S_3; (3) the higher wave of R_1 and S_3; (4) the amplitude of the QRS complex in its taller lead, i. e., the sum of R_1 and S_1 or of R_3 and S_3, and (5) $(R_1 + S_3) - (S_1 + R_3)$.[11]

The results are presented in table 1. It was found that criterion 2 is the most efficient, followed by 5 and then by 3 or 4 indifferently, while criterion 1 seemed poorest. Since the sum of R_1 and S_3 was found to be most valuable, consideration of voltage may be confined to this measurement.

Even with adequate data it is difficult to place an arbitrary dividing line as to just what sum of R_1 and S_3 should be considered abnormal. In 85 per cent of normal subjects with left axis deviation $R_1 + S_3$ was less than 1.9 millivolts, in 90 per cent less than 2.0 millivolts, in 95 per cent under 2.2 millivolts, in 99 per cent under 2.5 millivolts and in 99.9 per cent less than 2.9 millivolts. On the other hand, these values were exceeded in a vastly greater percentage of subjects with left ventricular hypertrophy. Thus the sum of R_1 and S_3 exceeded 2.5 millivolts in only 1 per cent of normal subjects with left axis deviation, whereas this amplitude was exceeded by 52 per cent of subjects with left ventricular hypertrophy. It may therefore be regarded that when the amplitude of $R_1 + S_3$ exceeds 2.5 millivolts hypertrophy is almost certainly present, when the sum exceeds 2.2 millivolts hypertrophy probably is present and that even a sum exceeding 2.0 millivolts suggests the likelihood of left ventricle hypertrophy.

High amplitude of the QRS complex not only occurs in the presence of marked hypertrophy but is an early change in left ventricular hypertrophy. This is indicated by the frequent occurrence of high amplitude among the intermediate group of 380 applicants for insurance notable only for elevated blood pressure, who may be considered as a mixed group composed largely of persons in the early stages of hypertension, as well as in small part persons in the later stages of the disease. It is of interest that 44.2 and 29.2 per cent of this mixed group fell above the 95 per cent (2.2 millivolts) and 99 per cent (2.5 millivolts) levels, respectively, of the normal curve.

Characteristic abnormalities in the terminal deflection of the ventricular complex, i. e., changes in the ST segment and the T wave, occur commonly in the presence of left ventricular hypertrophy. In the material studied these were not observed as frequently as increased amplitude of the QRS complex, and it appears that the changes in the ST segment and the T wave do not develop as early as increased voltage.

The changes in the ST segment and the T wave are less specific than increase in the amplitude of the QRS complex, since such changes occur in a great variety of conditions other than hypertrophy. It is generally stated that depression of the ST segment is significant if it is 1 mm. or more (0.1 millivolt) below the isoelectric baseline.[3] However, analysis of the electrocardiograms of the 460 normal subjects with left axis deviation disclosed none with any noticeable depression of the ST segment in lead I, whereas this occurred frequently among the subjects with left ventricular hypertrophy. We, therefore, regard depression of the ST segment in lead I of any perceptible degree, i. e., as little as 0.5 mm., as suggestive of left ventricular hypertrophy in the presence of hypertension with left axis deviation. Caution must be exercised in interpreting the position of the ST segment when there is tachycardia or a prominent U wave. Flattening of the T wave to an amplitude of less than 1 mm. or further degrees of abnormalities of the T wave in lead I likewise are to be considered suggestive of left ventricular hypertrophy when associated with left axis deviation in subjects with hypertension, since this was not observed among normal subjects. The depression of the ST segment and T wave negativity in lead I are accompanied by reciprocal elevation in lead III. As has been noted, while these changes are not specific for hypertrophy, nevertheless the pointed inversion of the T wave in lead I and the reciprocal relation of the terminal deflections in leads I and III are quite characteristic. In more advanced stages of left ventricular enlargement, as is well known, changes occur in the terminal deflections in lead II similar to, though less in degree than, those in lead I.

3. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Heart Association, 1939.

Characteristic changes in serial precordial leads occur in association with left ventricular enlargement as described by Wilson.[4] These were not investigated in the present study, since serial precordial leads were not made. Lowering of the initial positive deflection in lead CF_4 was observed frequently in the presence of marked left ventricular enlargement. This may possibly be due to the fact that in marked left ventricular enlargement the precordial electrode in lead CF_4 bears about the same relation to the left border of the heart that normally exists in lead CF_2, when the initial positive deflection is usually rather small.

The results of our study may be briefly summarized as follows: Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following abnormalities in the ventricular complex:

1. Increase in the amplitude of the QRS complex, when the sum of the R wave in lead I and the S wave in lead III is over 2.5 millivolts. Hypertrophy is probably present if this sum exceeds 2.2 millivolts and is suggested when the sum exceeds 2.0 millivolts.

2. Depression of the ST segment in lead I of any perceptible degree, even as slight as 0.5 mm. (0.05 millivolts).

3. Flattening of the T wave below 1 mm. amplitude or further degrees of abnormality of the T wave in lead I.

TABLE 2.—*Comparison of Electrocardiograms and Teleoroentgenograms for One Hundred Subjects with Advanced Hypertensive Disease*

	Percentage of Subjects
Electrocardiogram	
Pattern of hypertrophy	66
Evidence of myocardial disease	11
Total abnormalities	77
Teleoroentgenogram	
Apex outside midclavicular line	52
Transverse diameter more than 10 per cent above that predicted	41
Cardiothoracic ratio above 50 per cent	86

COMPARISON OF ELECTROCARDIOGRAPHIC AND ROENTGEN CHANGES ASSOCIATED WITH HYPERTROPHY

Employing these criteria rather than the well known advanced pattern associated with marked left ventricular enlargement, a study was carried out to determine the relative value of the electrocardiogram in detecting left ventricular hypertrophy as compared with the roentgenogram. Analytic study was made of 100 subjects with advanced hypertensive heart disease, and the electrocardiographic and roentgen findings were compared. Three criteria were employed in estimating heart size in the teleoroentgenogram: the transverse diameter in relation to standards predicted from weight and height,[5] the relation of the apex to the left midclavicular line as seen in the roentgenogram and the cardiothoracic ratio. The results are presented in table 2.

It is evident, and this has not been sufficiently appreciated, that the electrocardiogram is valuable for detecting left ventricular hypertrophy and is more sensitive than the roentgenogram. This comparison is not intended, of course, to deprecate the importance of roentgen study, but it does emphasize the

4. Wilson, F. N.: Recent Progress in Electrocardiography and the Interpretation of Borderline Electrocardiograms, Proc. A. Life Insur. M. Dir. America **27**:96, 1937.

5. Ungerleider, H. E., and Clark, C. P.: A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on the Teleoroentgenogram, Proc. A. Life Insur. M. Dir. America **25**:84, 1938.

usefulness of electrocardiographic study in detecting early left ventricular hypertrophy. Electrocardiographic and roentgen changes do not necessarily parallel one another, and while electrocardiographic abnormalities occur relatively more frequently than roentgen changes, at times there may be definite evidence of left ventricular enlargement in the roentgenogram while the electrocardiogram is quite normal. Rounding of the left ventricular contour is suggestive of left ventricular hypertrophy even if the measurements are not perceptibly increased, as is often the case in the earlier stage of concentric hypertrophy.

MECHANISM OF ELECTROCARDIOGRAPHIC CHANGES

The findings of the present study, as well as of previous investigations on electrocardiographic changes associated with left ventricular hypertrophy, are the result of correlating empiric with clinical observations and, just as with most other aspects of clinical electrocardiography do not stem from theoretic considerations. Nevertheless, it is of great interest to consider the mechanism of the electrocardiographic changes associated with hypertrophy of the cardiac chambers.

AXIS DEVIATION

The association of an inverted QRS complex in lead III with left ventricular enlargement and an inverted QRS complex in lead I with right ventricular enlargement was noted by Einthoven and other investigators, and the terms left and right ventricular preponderance came into common usage as an expression of deviation of the electrical axis. While it has been well recognized for some time that axis deviation is determined by factors other than ventricular hypertrophy, the terms left and right ventricular preponderance continue to be widely and improperly employed as synonymous with left and right axis deviation.

Certainly it cannot be denied that the deviation of the electrical axis is influenced by cardiac enlargement and that left axis deviation is a usual concomitant of left ventricular hypertrophy. However, that left ventricular hypertrophy is the determining factor in producing left axis deviation even in normal subjects [6] appears untenable in view of the well known fact that left axis deviation is readily produced by transverse position of the heart without relation to heart size, by factors which elevate the diaphragm, such as expiration, pregnancy and ascites, or by body build. Indeed, there is strong reason to believe that in hypertension, which is the commonest cause of left ventricular hypertrophy, position of the heart plays a determining role in accounting for left axis deviation apart from the factor of hypertrophy itself. The occurrence of left axis deviation in association with hypertrophy has been attributed to clockwise rotation of the heart on its longitudinal axis.[7]

The body build of subjects with hypertension is most frequently the obese heavy set type, in which left axis deviation occurs normally because of a transverse position of the heart. This association is clearly shown by analysis of the occurrence of left axis deviation in relation to body build in 422 subjects with hypertension.

It is evident that among underweight subjects with hypertension, who constitute a minority, left axis deviation is less commonly encountered but increases in direct proportion to the degree of overweight. Left axis deviation was encountered in a total of 78 per cent of subjects with hypertension, and an identical figure,

6. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, Philadelphia, Lea & Febiger, 1939, pp. 15 and 30.

7. van Nieuwenhuizen, C. L. C., and Hartog, H. A. P.: The Electrocardiogram in Hypertension with Especial Reference to Lead IV, Am. Heart J. **13**:308, 1937.

of 78 per cent, was found for another series of 100 subjects with advanced hypertensive heart disease. Other investigators have reported left axis deviation in a similar or slightly lower percentage of cases.

It is apparent, on the one hand, that left axis deviation is closely related to body build and, on the other, that left axis deviation is not a necessary and invariable accompaniment of left ventricular hypertrophy. One does not imply that left axis deviation is entirely unrelated to left ventricular hypertrophy, for there is no doubt that left ventricular hypertrophy of itself is capable of producing left axis deviation, while conversely right ventricular hypertrophy ensuing late in the course of hypertensive disease tends to nullify the electrical effects of left ventricular hypertrophy and may cause left axis deviation to disappear. It may be stated, however, that left axis deviation does not seem to be an essential part of the electrocardiographic pattern of left ventricular hypertrophy. Other characteristic features of the electrocardiographic pattern in left ventricular hypertrophy, in the terminal deflections of the ST segment and the T wave, may evolve prior to or even in the absence of left axis deviation, as has been noted by Kaplan and Katz [8] and Barnes.[9] It has been our experience that this is particularly apt to occur in subjects of normal or of slender build, more often in association with left ventricular hypertrophy due to aortic insufficiency, nephritic hypertension or malig-

TABLE 3.—*Relation of Axis Deviation to Body Build in Four Hundred and Twenty-Two Applicants for Insurance with Hypertension*

Percentage Deviation from Average Weight	Number of Subjects	Subjects with Left Axis Deviation	
		Number	Percentage
—20 or less	1	1	
—20 to —11	9	3	33
—10 to — 1	41	21	51
0 to + 9	103	68	66
+10 to +19	147	123	84
+20 or over	121	114	94
	422	330	78

nant nephrosclerosis. While these changes in the terminal deflection do occur in the absence of left axis deviation, they appear to evolve much more readily when left axis deviation is present, and the electrocardiogram appears to be somewhat less sensitive in detecting hypertrophy in subjects of slender stature.

The degree of left axis deviation does not bear any constant relation to the degree of left ventricular hypertrophy. While extreme left axis deviation where the QRS is completely inverted in lead II, as well as in lead III, is usually an abnormal finding, it does not indicate left ventricular hypertrophy but may denote an abnormal conduction pattern due to myocardial disease.

VOLTAGE

Voltage in the electrocardiogram is determined by several factors: the mass of cardiac muscle; the relation between the excitation process in the two ventricles; the position of the heart determining the direction of potential, and conduction through the body tissues to the electrodes. The last factor probably accounts for high voltage in leads taken directly over the precordium and the relatively high voltage which may be observed in children, but it has no bearing on changes in voltage associated with hypertrophy. Position of the heart is not a significant

8. Kaplan, L. G., and Katz, L. N.: The Characteristic Electrocardiograms in Left Ventricular Strain With and Without Axis Deviation, Am. J. M. Sc. **201**:676, 1941.

9. Barnes, A. R.: (*a*) Electrocardiographic Patterns, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 77; (*b*) pp. 66-67.

factor in explaining the high voltage in left ventricular hypertrophy, for voltage in the limb leads could not be related to body build in the 460 normal subjects with left axis deviation. An altered relation between the time of development of the excitation process in the two ventricles is responsible for the high voltage in ventricular extrasystoles and in bundle branch block. This factor, however, can hardly explain the high voltage in left ventricular hypertrophy, since the excitation process is most often normal in left ventricular hypertrophy and the QRS complex is not appreciably widened until an advanced stage, when bundle branch block may supervene. It appears, therefore, that the increased voltage is to be ascribed directly to an increased mass of left ventricular musculature. It should be noted, however, that increased voltage, particularly of the R wave in lead I was observed by Robb and Robb [10] as an immediate consequence of acute left ventricular strain where hypertrophy could play no part.

It may be emphasized again that high voltage of the QRS complex is the earliest and most frequent electrocardiographic change associated with left ventricular hypertrophy. The study has indicated the limits of normal voltage in the presence of left axis deviation. It is generally stated that voltage is abnormal if the QRS in the tallest lead exceeds 2.0 millivolts.[11] Our study, however, indicates the necessity of judging voltage in association with axis deviation. In the absence of left axis deviation, high voltage is of no significance. Voltage as high as 2.5 or even 3.0 millivolts, most frequently in leads 2 and 3, may be observed normally when left axis deviation is not present, particularly in young slender subjects. In association with left axis deviation much lower amplitudes of the QRS complex are vastly more significant, as has been indicated.

ABNORMALITIES OF THE ST SEGMENT AND THE T WAVE

There has been much speculation concerning the cause of the changes in the ST segment and the T wave associated with ventricular hypertrophy, and several explanations have been suggested. These changes have been ascribed by some investigators to hypertrophy itself,[12] which is assumed to result in an altered relation between the electrical potential of the two ventricles. It has been suggested that the conduction pathway is impaired [13] or lengthened owing to enlargement of the left ventricle with delay in excitation of the left ventricular myocardium. The similarity of the electrocardiographic patterns in left ventricular hypertrophy with those of left bundle branch block is cited as support of the hypothesis that impaired conduction through the left bundle branch is responsible for the changes in hypertrophy.[14] If this were the mechanism, it might be expected that the width of the QRS complex, which measures the duration of the excitation process, would be similarly prolonged, as it is in bundle branch block. Actually, the QRS complex is usually of relatively normal duration, except in the more advanced stages of enlargement. Characteristic changes in the ST segment and the T wave are frequently observed with QRS complexes of normal width.[15] It is highly improb-

10. Robb, J. S., and Robb, R. C.: Hypertension Electrocardiograms Experimentally Produced and Anatomically Explained: II. Left Ventricular Strain, Am. J. M. Sc. **203**: 634, 1942.

11. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram Including the Cardiac Arrhythmias, ed. 4, New York, Paul B. Hoeber, Inc., 1941, p. 48. Footnote 3.

12. Master, A. M.: Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension: Their Prognostic Significance, Am. Heart J. **5**:291, 1930.

13. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941, p. 291.

14. Master,[6] p. 108.

15. Rykert, H. E., and Hepburn, J.: Electrocardiographic Abnormalities Characteristic of Certain Cases of Arterial Hypertension, Am. Heart J. **10**:942, 1935.

able that lengthening of the conduction pathway is responsible for the electrocardiographic changes, since advanced changes in the ST segment and the T wave may be observed when the ventricular cavity is not enlarged during the stage of concentric hypertrophy, while the terminal deflections may be quite normal when the left ventricle is markedly dilated and the conduction pathway presumably lengthened, as in cases of aortic insufficiency.

Recently Robb and Robb [10] have attempted to relate the changes in the ST segment and the T wave to strain produced by stretching of the individual bundles of muscle, which they stated involves the superficial layers to the greatest degree:

> The left ventricle is enclosed by four muscle masses which give way in sequence: the superficial sinospiral first, the superficial bulbospiral next, later the deep sinospiral, and in extremis the deep bulbospiral muscle.

The characteristic depression of the ST segment in lead I with elevation in lead III is ascribed by these authors to involvement of the superficial bulbospiral muscle.

Certain pathologic and physiologic considerations suggest, however, that the characteristic electrocardiographic changes result from ischemia of the inner layers of the left ventricle rather than from involvement of the superficial bundles of muscle. If the greatest strain were placed on the superficial layers of muscle in hypertrophy, one would expect to find the greatest degree of pathologic change in this region. While the portions of the superficial sinospiral and bulbospiral muscles which curve inward to form the papillary muscles are frequently involved, the outer layers of the left ventricular myocardium are usually relatively normal, whereas diffuse involvement is regularly observed in the deeper layers of the left ventricle, particularly the subendocardial region. This vulnerability of the subendocardial region has been emphasized by Büchner and associates [16] and has been noted by Friedberg and Horn [17] and by one of us (R. G.) in collaboration with Master, Dack and Jaffe in a study of 48 cases of fatal coronary insufficiency.[18]

Depression of the ST segment and abnormalities of the T wave similar to those encountered in hypertrophy occur regularly in association with a great variety of clinical and experimental conditions which cause pathologic changes in the inner subendocardial layer of the left ventricle. Among these may be mentioned acute and chronic anemia, carbon monoxide poisoning, shock, overexertion, anoxemia and mechanical trauma to the endocardium. When a condition such as acute anemia or other strain occurs in a subject with early hypertrophy, a latent electrocardiographic pattern of left ventricular hypertrophy may be brought out, which suggests that similar mechanisms are operative in evoking the electrocardiographic changes.

It has been suggested because of the similarity of the changes in the ST segment and the T wave associated with hypertrophy to those observed in myocardial ischemia in more acute states that the abnormalities of the ST segment and the T wave represent a chronic metabolic strain.[19] There are several factors which may contribute to produce a relative inadequacy of coronary supply in

16. Büchner, F.; Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsuffizienz in vergleichender elektrokardiographischer und morphologischer Untersuchung, Leipzig, Georg Thieme, 1935.

17. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675 (April 29) 1939.

18. Master, A. M.; Gubner, R.; Dack, S., and Jaffe, J. L.: Differentiation of Acute Coronary Insufficiency with Myocardial Infarction from Coronary Occlusion, Arch. Int. Med. **67**:647 (March) 1941.

19. Barnes, A. R., and Whitten, M. B.: Study of T Wave Negativity in Predominant Ventricular Strain, Am. Heart J. **5**:14, 1929.

hypertrophy. While the increased aortic pressure tends to augment coronary flow, it does not do so in proportion to the greatly increased work performed by the left ventricle. The capillary count per square millimeter, which is the true measure of blood supply, is relatively decreased in hypertrophy, as has been shown by Wearn.[20] Furthermore, increased thickness of the hypertrophied muscle cells makes difficult rapid diffusion of oxygen, nutriments and metabolites. In addition to these factors which tend to cause a relative inadequacy of coronary flow there is often added an absolute reduction in coronary flow due to associated coronary artery disease, particularly when hypertension is present. Changes in the ST segment and the T wave associated with hypertension have been ascribed directly to coronary artery sclerosis,[21] but these changes occur as well in the absence of any significant coronary artery disease in hypertension.[15] Aortic stenosis and insufficiency, which also are frequent causes of left ventricular hypertrophy, likewise operate to reduce the absolute coronary flow. Further evidence that the changes in the ST segment and the T wave are due to a metabolic strain is suggested by the fact that the changes are reversible. These abnormalities have been observed to diminish or disappear promptly in cases in which marked lowering of blood pressure has attended therapy of hypertension by various measures, such as sympathectomy [9] and administration of thiocyanates, renal extracts and tyrosinase.

While these factors give adequate reason to believe that a relative coronary insufficiency is responsible for the electrocardiographic changes in hypertension, there is yet one other factor which appears to be important particularly in explaining the localization of myocardial involvement in the deeper layers of the left ventricle. It is involvement of this region which produces the characteristic electrocardiographic changes.

Johnson and Di Palma [22] have recently shown that there is a marked gradient in intramyocardial pressure from the epicardium to the endocardium. While the intramural pressure of external layers of the left ventricle does not rise high during systole, the pressure in the deeper layers of the left ventricular musculature rises to very high levels during systole, far above the aortic pressure. There must, therefore, be a complete arrest of flow in the coronary vessels supplying the subendocardial region of the left ventricle during a portion of systole. In the outer layers of the left ventrticle coronary flow is not arrested during systole because the intramyocardial pressure is not as high. The superficial layers may receive a relatively greater supply because of diversion of blood flow from the deeper layers, where systolic flow is impeded. The earlier observations of Anrep and Saalfeld [23] suggested a complete cessation of flow in systole. While more recent studies [24] have indicated that some degree of intramural systolic inflow does occur, yet this may be shunted to the outer layer in the manner suggested. In the right ventricle and in the auricles the intramyocardial pressure during systole is much lower than the pressure within the coronary artery, and so coronary flow is not impeded during systole in these chambers. It is thus evident that the

20. Wearn, J. T.: Morphological and Functional Alterations of the Coronary Circulation, Bull. New York Acad. Med. **17**:754, 1941.

21. Levine, S. A.: Clinical Heart Disease, ed. 2, Philadelphia, W. B. Saunders Company, 1940, p. 161.

22. Johnson, J. R., and Di Palma, J. R.: Intramyocardial Pressure and Its Relation to Aortic Blood Pressure, Am. J. Physiol. **125**:234, 1939.

23. Anrep, G. V., and Saalfeld, E. V.: The Effect of Cardiac Contraction upon the Coronary Flow, J. Physiol. **79**:317, 1933.

24. Gregg, D. E.: Phasic Changes in Flow Through Different Coronary Branches, in Blood, Heart and Circulation, Publication 13, American Association for the Advancement of Science, 1940, p. 81.

efficiency of the coronary circulation is poorest in the subendocardial region of the left ventricle, since flow is cyclic rather than continuous. This region will be the one to suffer most from ischemia by any reduction in coronary flow or increased oxygen requirements of the myocardium. Pathologic confirmation of the relative inefficiency of the coronary circulation in the deeper layers of the left ventricle is afforded by the observations of Mallory, White and Salcedo-Salgar.[24a] These investigators noted that subendocardial infarcts heal less rapidly than those in the center of the myocardium or beneath the epicardium and are poorly vascularized.

This factor explains the vulnerability of the subendocardial region of the left ventricle in hypertrophy and the predilection of myocardial disease for this region in a great variety of pathologic states, whereas involvement of the outer layers of the left ventricle, the right ventricle and the auricles is relatively infrequent. When intraventricular pressure in the right ventricle is markedly elevated, as in pulmonic hypertension secondary to mitral disease, coronary flow may be impeded during systole [25] with ischemia and damage to the subendocardial region of the right ventricle, producing the characteristic changes in the ST segment and the T wave in leads III and II.

In case of prolonged coronary insufficiency degeneration of cardiac muscle occurs, with replacement fibrosis. This is most marked in the subendocardial region of the left ventricle, where the metabolic strain is greatest. The fibrosis may involve the Purkinje network, which ramifies in the subendocardium, either directly or by impairing the vascular supply. This results in abnormal conduction, with the appearance of slurring, notching and widening of the QRS complex, eventually progressing to the pattern of left bundle branch block, which is frequently encountered in long-standing and advanced left ventricular enlargement. The widening of the QRS complex in hypertrophy is only in slight part attributable directly to increased thickness of the left ventricular myocardium. Oppenheimer and Rothschild [26] showed that in cases of bundle branch block there are widely disseminated areas of patchy sclerosis of the subendocardial region. To quote their classic study,

> The pathologic changes, especially the sclerosis, predominate in the endocardial and subendocardial layer, that is, in the region of the so-called Purkinje network, as compared with the outer two thirds of the ventricular musculature.

Left bundle branch block is much more common than right bundle branch block because the subendocardial region of the left ventricle is predominantly involved in myocardial disease. The pattern of right bundle branch block may evolve by a similar mechanism in long-standing right ventricular enlargement secondary to mitral valvular disease, chronic cor pulmonale and certain types of congenital heart disease, such as pulmonic stenosis, which place a strain on the right ventricle.

TERMINOLOGY OF ELECTROCARDIOGRAPHIC CHANGES

A conspicuous lack of uniformity exists in the nomenclature employed to describe the electrocardiographic patterns associated with left ventricular hypertrophy. Various terms, such as left ventricular strain, left ventricular preponderance, hypertrophy and enlargement, are employed. It would seem desirable that

24a. Mallory, G. K.; White, P. D., and Salcedo-Salgar, J.: The Speed of Healing of Myocardial Infarction, Am. Heart J. **18**:647, 1939.

25. Visscher, M. B.: The Restriction of the Coronary Flow as a General Factor in Heart Failure, J. A. M. A. **113**:987 (Sept. 9) 1939.

26. Oppenheimer, B. S., and Rothschild, M.: Electrocardiographic Changes with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

a more uniform terminology be adopted in describing and interpreting the electrocardiographic changes. Certain terms, such as left ventricular preponderance, are confusing, since this description is often used interchangeably with left axis deviation, which of itself, of course, is not indicative of left ventricular hypertrophy.

Based on the genesis of the electrocardiographic abnormalities suggested here, the following terminology appears more specifically descriptive of the anatomic changes in the left ventricle.

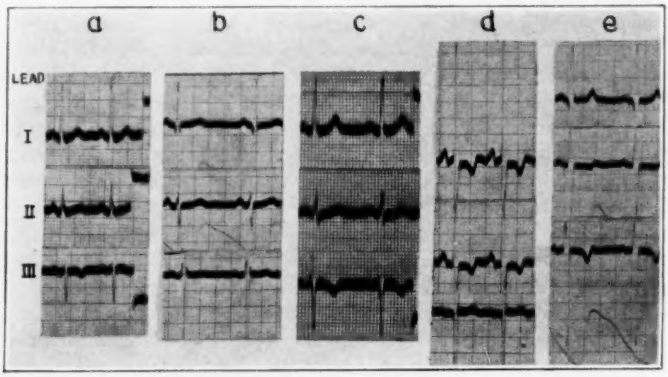

Fig. 1.—Left ventricular hypertrophy. Left axis deviation associated with high voltage of the QRS complex. (*a*) A high R_1, just exceeding normal limits. (*b*) A deep S_3. (*c*) The sum of R_1 and S_3 exceeds 2.5 millivolts. (*d*) An extremely high R_1. (*e*) An extremely deep S_3.

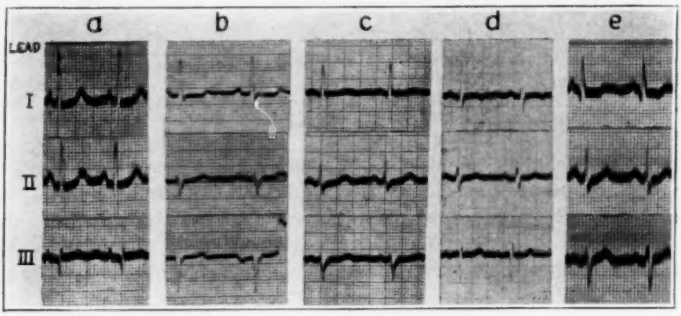

Fig. 2.—Left ventricular strain. Left axis deviation associated with changes in the ST segment and the T wave. (*a*) A slight depression of the ST segment in lead I. (*b*) A depression of the ST segment in lead I and a reciprocal elevation in lead III. (*c*) A low T_1. (*d*) An inverted T_1. (*e*) A depressed ST segment and a diphasic T wave in lead I.

Left Ventricular Hypertrophy.—This term may be employed appropriately where left axis deviation is associated with increased amplitude of the QRS complex (the sum of R_1 and S_3 exceeds 2.5 millivolts or R_1 or S_3 individually exceeds 1.6 millivolts). The high voltage pattern is illustrated in figure 1.

Left Ventricular Strain.—This term should be employed when characteristic changes are present in the ST segment and the T wave in the absence of high voltage (fig. 2) or in the absence of left axis deviation (fig. 3). The changes in

the ST segment and the T wave are less specific of hypertrophy than is high voltage. While characteristic changes in the terminal deflections are usually associated with left ventricular hypertrophy, similar abnormalities may occur in conditions other than hypertrophy when a metabolic strain is placed on the left ventricle (e. g., anemia). Well marked changes in the ST segment and the T wave may be present in the absence of high voltage of the QRS complex, and high voltage of the QRS complex may not infrequently disappear in the later stages of left ventricular hypertrophy with diffuse myocardial disease or after myocardial infarction.

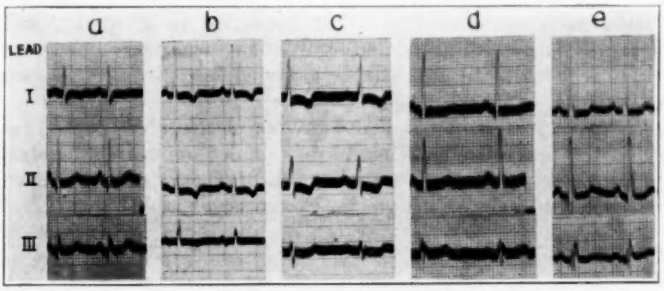

Fig. 3.—Left ventricular strain. Changes in the ST segment and the T wave in the absence of left axis deviation. (*a*) A diphasic T_1. (*b*) Inverted T_1 and T_2. (*c*) A depressed ST segment and an inverted T wave in lead I and lead II. There is a slight tendency to left axis deviation. (*d*) A tall R wave, a depressed ST segment and a diphasic T wave in lead I. (*e*) A tall R wave and a depressed ST segment in lead I.

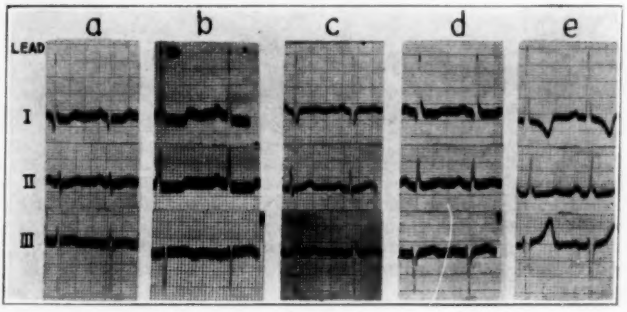

Fig. 4.—Left ventricular hypertrophy and strain. (*a*) A high voltage QRS complex, with the ST segment depressed in lead I and elevated in lead III. (*b*) A high R_1, a depressed ST segment in lead I and lead II and an elevated ST segment in lead III. (*c*) A high voltage QRS complex and a diphasic T wave in lead I. (*d*) A high voltage QRS complex, a depressed ST segment and an inverted T wave in lead I. (*e*) A typical pattern, with a high voltage QRS complex and characteristic changes in the ST segment and the T wave.

Left Ventricular Hypertrophy and Strain.—This term should be used to connote more advanced electrocardiographic changes when both the patterns of hypertrophy (high voltage of the QRS complex) and metabolic strain (changes in the ST segment and T wave) are present (fig. 4).

Left Ventricular Hypertrophy with Myocardial Strain and Fibrosis (fig. 5).—The final stage of left ventricular enlargement as revealed in the electrocardiogram includes, in addition to the aforementioned changes in QRS voltage and terminal deflections, abnormalities in the QRS complex, such as slurring, notching and

widening, progressing ultimately in its most advanced form to the pattern of left bundle branch block. These abnormalities in the QRS complex are considered to represent diffuse myocardial fibrosis ensuing after long-standing left ventricular strain, which involves the conduction system interfering with the excitation process.

The electrocardiographic patterns described do not always have an exact anatomic counterpart, for the pattern of left bundle branch block occasionally may be produced by localized involvement of the left main bundle branch in the interventricular septum without any necessary left ventricular disease otherwise. The pattern of left bundle branch block (fig. 5 *e*) is encountered, too, in normal persons with a short PR interval, who are subject to attacks of paroxysmal tachycardia (Wolff-Parkinson-White syndrome). The pathogenesis of bundle branch block in such instances is not related to left ventricular enlargement or to myocardial disease but is believed to be due to aberrant conduction from the auricles to the ventricles.

While it may appear unwarranted to relate electrocardiographic patterns so specifically to the degree of anatomic change, a definite correlation between the severity of the electrocardiographic changes and prognosis has been demonstrated.[2] The criteria proposed indicate the precise electrocardiographic changes which may

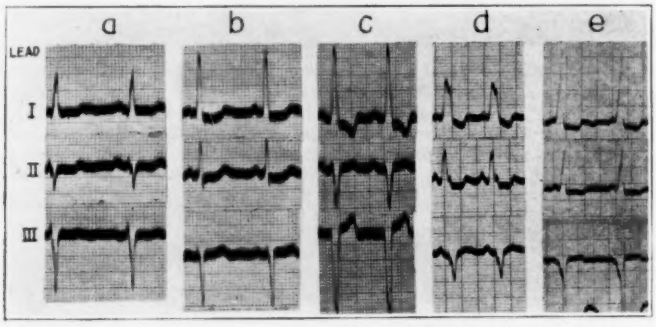

Fig. 5.—Left ventricular hypertrophy with myocardial strain and fibrosis. (*a*) A deep S_3 and a depressed ST segment and a diphasic T wave in lead I. The QRS complex is slurred and notched. (*b*) A high voltage and depressed ST segment in lead I and lead II. R_1 is notched. (*c*) Typical changes in voltage and terminal deflection. The QRS complex is widened to twelve hundredths of a second. (*d*) Left bundle branch block. The QRS complex is notched and widened to thirteen hundredths of a second. (*e*) Left bundle block with a short PR interval. This is not due to left ventricular hypertrophy but is an anomaly of conduction.

be considered diagnostic of hypertrophy, and the graded terminology of the more advanced changes further provides an approximate estimate of the degree of left ventricular enlargement, which is more graphic than any single phrase, such as left ventricular preponderance.

SUMMARY

An electrocardiographic diagnosis of left ventricular hypertrophy can be made before advanced changes have occurred. Employing criteria established by a study of a large number of normal subjects and persons with hypertension, we found that the electrocardiogram is a valuable device for detecting left ventricular hypertrophy and is somewhat more sensitive than the teleoroentgenogram. The electrocardiographic and roentgen changes do not necessarily parallel one another, and at times either may be relatively normal, while the other shows definite evidence of hypertrophy.

Left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following changes:

1. Increase in amplitude of the QRS complex, best expressed by the sum of R_1 and S_3. Hypertrophy is present if this sum exceeds 2.5 millivolts and is probably present if it is over 2.2 millivolts. The increase in voltage is the earliest electrocardiographic change in hypertrophy.

2. Any perceptible depression of the ST segment in lead I, even of as slight degree as 0.5 mm. (0.05 millivolt).

3. Lowering of T_1 below 1 mm. or further degrees of abnormality of T_1.

The changes in the ST segment and the T wave may develop in the absence of left axis deviation, and left axis deviation is not an invariable or necessarily integral part of the electrocardiographic pattern of left ventricular hypertrophy. It is shown that the usual occurrence of left axis deviation with left ventricular hypertrophy in hypertension is due largely to predominant obesity with transverse position of the heart, which in itself causes left axis deviation. In slender subjects with left ventricular hypertrophy left axis deviation is not so often observed.

The increased amplitude of the QRS complex may most reasonably be attributed directly to an increased mass of left ventricular musculature. The changes in the ST segment and the T wave are regarded as due to relative ischemia of the deeper layers of the left ventricle. This is occasioned by increased work of the heart without commensurate increase in coronary flow. Several factors, which are discussed, contribute to cause this disproportion.

The particular vulnerability of the subendocardial region of the left ventricle is due to an intramyocardial pressure gradient during contraction. During systole there is a marked increase in intramyocardial pressure in the deeper layers of the left ventricle, which exceeds aortic pressure and which obstructs coronary flow in this region, although there is no interference in coronary flow in the outer zone of the left ventricle or in the right ventricle or auricles, where the intramyocardial pressure does not rise above the arterial pressure. The subendocardial region of the septum and the left ventricle on this account is the area most vulnerable to ischemia. It is the site of predilection of myocardial disease when there is a relative insufficiency of coronary flow, as in hypertrophy, or when there is an absolute decrease in flow, as in coronary artery sclerosis and acute coronary artery occlusion.

Over a long period, the chronic subendocardial ischemia leads to irreversible changes and replacement fibrosis occurs. This involves the Purkinje distribution network of the left bundle branch which ramifies in the subendocardial region of the interventricular septum and the left ventricle. Interference with left ventricular excitation caused by diffuse involvement of the conduction system leads to slurring, notching and widening of the QRS complex, eventually progressing to the pattern of left bundle branch block, which is frequently encountered in association with long-standing and advanced left ventricular enlargement. The widening of the QRS complex is only in slight part attributable directly to increased thickness of the left ventricular myocardium.

Changes in the ST segment and the T wave in leads II and III, and ultimately right bundle branch block, occur in conditions associated with chronic right ventricular strain, such as pulmonic stenosis, cor pulmonale and long-standing mitral disease. The pathogenesis of these changes, just as in left ventricular hypertrophy, is similarly related to ischemia of the subendocardial region of the right ventricle consequent to increased intraventricular pressure in the right ventricle.

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THE QRS COMPLEX OF THE ELECTROCARDIOGRAM

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The electrocardiogram is a photographic record of the differences in electrical potential existing between two points on the body surface at every instant during the time the record is being taken. On the ordinates of the record one reads the potential differences; on the abscissas the time is given. When the electrocardiogram in the three standard limb leads is made, measurement of the potential differences at any instant in any two leads supplies data from which one may calculate the apparent direction and magnitude of the electromotive force at that instant as that force is projected on the frontal plane of the body. The direction of the force at each instant is the instantaneous electrical axis. Since the electromotive force has both direction and magnitude, it is a vector quantity. One may determine the magnitudes and directions of the vectors for each instant of the ventricular (or auricular) electrocardiogram and draw lines on paper representing them. If they are drawn in sequence so that they radiate from a common center, the distal ends of the vectors will describe a path which is known as the vectorcardiogram.[1] It is, indeed, possible to record this path directly by special apparatus.[1]

The use of vector analysis does not necessarily imply that the directions of the vectors are their true directions relative to the frontal plane. Such analysis is capable of extensive application and is useful, even though the directions as recorded are in error. Yet it has been widely assumed, if not by Einthoven, at least by many electrocardiographers, that the direction of the electrical axis is a true representation of the orientation of the electromotive force, relative to the frontal plane. The validity of this assumption has been denied by Katz,[2] by Wolferth, Livezey and Wood [3] and by others. Since we have tentatively accepted the validity of the Einthoven triangle hypothesis, at least as a close approximation, we cannot ignore the attack on it, and we shall return to it later.

The present paper deals with an attempt to explain the QRS complex in human beings in terms of successive stages of invasion of the ventricular muscle by the wave of excitation. Our method involves vector analysis. The value of this method has been greatly impaired by the difficulty of knowing the normal sequence of activation of the ventricular muscle. Although we may choose any instant during the course of that activation and calculate a vector representing the direction and magnitude of the electromotive force at that instant, we are unable to interpret the vector in terms of the particular region or regions of cardiac muscle which are becoming active at the chosen instant. If we await more precise, directly acquired knowledge of the sequence of ventricular activation in man, it is clear that we shall have to

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1. Wilson, F. N., and Johnston, F. D.: The Vectorcardiogram, Am. Heart J. **16**:14, 1938.

2. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941; Concerning a New Concept of the Genesis of the Electrocardiogram, Am. Heart J. **13**:17, 1937.

3. Wolferth, C. C.; Livezey, M. M., and Wood, F. C.: Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, Am. J. M. Sc. **203**:641, 1942.

wait indefinitely. For that reason, we are compelled to take the electrocardiogram as it is recorded for a human being and to determine whether it is the picture which would necessarily be produced if the human ventricles are activated essentially in the same manner and sequence as the ventricles of the experimental animal. Fortunately, we now have access to reliable experimental observations, such as those of Lewis,[4] Eyster and Meek,[5] Harris [6] and also Nahum, Hoff and Kaufman,[7] which may be reinterpreted as necessary and applied to our problem. In certain details, for which experimental evidence on human beings is lacking, we have been compelled to infer the sequence of ventricular excitation from the electrocardiogram itself.

THE EXPERIMENTAL BASIS OF OUR PRIMARY ASSUMPTIONS

Every student of electrocardiography is familiar with the conclusions of Lewis and Rothschild [8] with respect to the sequence of activation of the ventricles in human beings. The wave of excitation is delivered simultaneously to the two ventricles by way of the branches of the atrioventricular bundle. Through a subendocardial Purkinje network, at a velocity of 3 to 5 meters per second, the impulses reach the ventricular muscle proper. The two sides of the septum were regarded as being first to be activated; the apical subendocardial muscle as activated later, the lateral ventricular walls still later and the bases of the ventricles last. From the subendocardial surfaces the activity was supposed to spread outward, at a rate of 0.4 meter per second, almost radially to the subepicardial muscle. Since the left ventricle is much thicker than the right one, the last part of the ventricles to be activated was supposed to be the subepicardial muscle at the base of the left ventricle. In spite of attempts to break down this relatively simple picture, it has met the demands of electrocardiography in human beings remarkably well, though we have found it necessary to modify certain details. Harris [6] in a recent excellent paper reported on the sequence of activation of the epicardial surface of the cat, dog and monkey ventricles, together with some observations on the subendocardial activation and the time required for the impulse to penetrate the ventricular walls in the dog. One may infer from his work that the time required by the impulse to activate the subendocardial surface is possibly shorter than the time assumed by Lewis and Rothschild.[8] Furthermore, the epicardial surface of the pulmonary conus is activated late, at least as late as the basal lateral wall of the left ventricle, and this probably holds for man. In the monkey, the apical and anterior surface of the right ventricle near the interventricular groove is earliest to be excited, the apical and anterolateral apical region of the left ventricle being activated only slightly later. In 1 monkey the latter region on the left was excited as early as the early region of the right ventricle—and we suspect that this individual difference also occurs in man. In the dog the impulse appears to pass from endocardium to epicardium roughly in a radial fashion, as postulated by Lewis, though it is possible that the pulmonary conus may be activated by impulses traveling longitudinally in muscle

4. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925.

5. Eyster, J. A. E., and Meek, W. J.: The Sequence of Fractionate Contraction at Different Surface Regions on the Right Auricle and Ventricles of the Dog's Heart, Am. J. Physiol. **134**:513, 1941.

6. Harris, A. S.: The Spread of Excitation in Turtle, Dog, Cat and Monkey Ventricles, Am. J. Physiol. **134**:319, 1941.

7. Nahum, L. H.; Hoff, H. E., and Kaufman, W.: (*a*) Formation of the R Complex of the Electrocardiogram, Am. J. Physiol. **134**:384, 1941; (*b*) The Nature of the S Complex of the Electrocardiogram, ibid. **136**:726, 1942.

8. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart: The Ventricles, Phil. Tr. **206**:181, 1915.

bundles, as pictured by Robb and Robb.[9] In the dog's left ventricle the time for impulse conduction from the endocardial to the epicardial surface is about 0.02 second. In the right ventricle the time is much less. The rather early activation of the epicardial surface of the anteroapical portion of the left ventricle may depend on Purkinje fiber pathways dipping into the wall, especially in the monkey. Since man is also a primate, this may also be true of man. Certain facts, particularly the behavior of the Q wave in right bundle branch block, have forced us to the conclusion that the subendocardial walls of the septum, especially on the right, are poorly supplied by connections between the Purkinje network and the myocardium proper. Hence, although septal activation may start early in places, general activation of the septal surfaces may be later than activation of the subendocardial apical surfaces. Similarly, the pulmonary conus, and possibly the basal rim of the left ventricle, may be poorly supplied by a subendocardial Purkinje network. Because of the early activation of the subepicardial muscle adjoining the anteroapical part of the interventricular groove, we have assumed either that subendocardial activation is earlier in these regions or that it is earlier to involve the whole inner muscular surface. We have carefully reviewed the valuable papers of Nahum and Hoff [7] and their co-workers. On reinterpretation of their results in terms of acceptable fundamentals we find nothing incompatible with the assumption we have made, except that the orientations of the surfaces we have assumed for man differ from those reported by Hoff and Nahum for the dog. Since they reported differences between the dog and the monkey, our assumption is not unlikely.

The sequences of ventricular activation which we have chosen for man are shown in the figures and need not be stated at this point. It is impossible here fully to recapitulate the fundamental postulates of electrocardiography, but a few points may be noted. When a wave of excitation is moving through a ventricular wall, positive charges are present in front of the wave and negative charges at its rear. The charges are close together. The electrical vector produced is drawn pointing from the negative electrical field to the positive electrical field, i. e., in the direction in which the impulse is progressing. The direction is accurately represented by having the vector point at right angles to the plane the margins of which are the boundary or edges of the polarized shell at the wave front of the excitation wave. The length of the vector is proportional to the area of the opening in the polarized shell. If two or more polarized shells are present, the combined magnitude and direction of these on the potentials of the limbs is the resultant effect of the two vectors, which is determined by application of the principle of the parallelogram of forces. Figure 1 and its legend attempt to make the foregoing points clear. The electrical fields are produced by the charges on the polarized shell, and the fields are distributed through the surrounding tissue, including both fully resting or polarized muscle or fully depolarized muscle. Neither a fully active nor an inactive ventricular wall produces electrical effects or makes any contribution to the electrical fields. In other words, each instantaneous electrical axis observed during inscription of the QRS complex is produced by the charges at the front of the depolarization wave and nowhere else.[10] The electrical dipoles, each with its positive and negative charge, which are responsible for the T wave, are distributed through the muscle, unlike the dipoles responsible for the QRS complex. This more difficult problem is not considered in the present paper. The way in which these postulates are applied to the problem will be clear from the

9. Robb, J. S., and Robb, R. C.: The Normal Heart: Anatomy and Physiology of the Structural Units, Am. Heart J. **23**:455, 1942.

10. Craib, W. H.: The Electrocardiogram, Medical Research Council, Special Report Series, no. 147, London, His Majesty's Stationery Office, 1930.

figures and their descriptions. We assume that the reader is conversant with the method of determining the direction of an electrical axis by the Einthoven equilateral triangle method. In the preparation of the figures which illustrate the text, observations were made on human hearts in situ as exposed at autopsy, and clay models were constructed to facilitate visualization of the spatial relations of the ventricular walls.

It may be pointed out that although we believe the dipole theory of production of the waves of the QRS complex to be the correct one, nevertheless, if the reader prefers to visualize the active muscle as electrically negative and the inactive muscle as electrically positive, the consequences, so far as indirect leads are concerned, will be the same, and the description given here will still apply.

SEQUENCE OF ACTIVATION OF HUMAN VENTRICULAR MUSCLE AND FORMATION OF THE QRS COMPLEX

Figures 2 through 7 illustrate the assumptions on which we have based our construction of the QRS complex in human beings. We may repeat that the

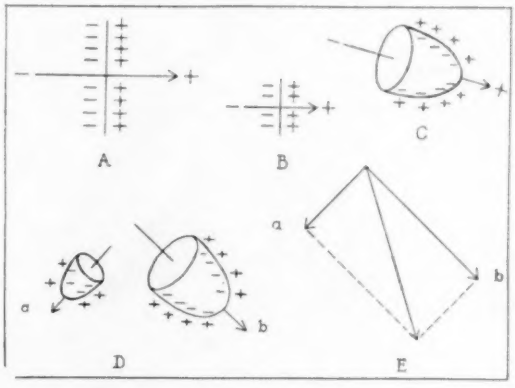

Fig. 1.—*A* and *B* show that the vector points from the negative side of the polarized membrane to the positive side and the length of the vector is proportional to the size of membrane (actual area), assuming the intensity of polarization is the same on the two. If the membrane is in muscle, the impulse is moving in the direction of the arrow. Current flow is from the positively charged side around through the external medium to the negatively charged side of the membrane. *C* shows that if the membrane, or shell, is curved like a cup, the vector points in at right angles to the plane of the opening in the cup and is proportional to the area of the opening. *D* shows two shells of unequal size. *E* illustrates the summation of the two vectors shown in *D* to produce the resultant vector.

sequence of activation as represented fits the facts of animal experimentation, but that experiment has not given all the facts needed. This is particularly true of activation of the interventricular septum.

The ventricles are shown as if rotated more on a longitudinal axis than is usual in the heart of a sthenic person. The direction of this rotation away from the average position is counterclockwise when the heart is viewed from the apex. This rotation, which is by no means uncommon for more transversely placed hearts, enables us to illustrate the regions being activated better than would be possible with a heart in the average position. The right ventricular wall is shown largely

cut away; there is a hole in the left ventricle above the apex, and another opening extends through the septum, so that its left ventricular surface can be represented in part, together with the right ventricular surface. The opening of the tricuspid valve appears as a dark oval. The valve leaflets, the papillary muscles and other detailed structures are not represented.

In figure 2 the impulse is shown to have invaded the right and the left surface of the septum, but it is assumed that the connections between the Purkinje system and the muscle are incomplete on the septal surfaces (Mahaim and Winston [11]).

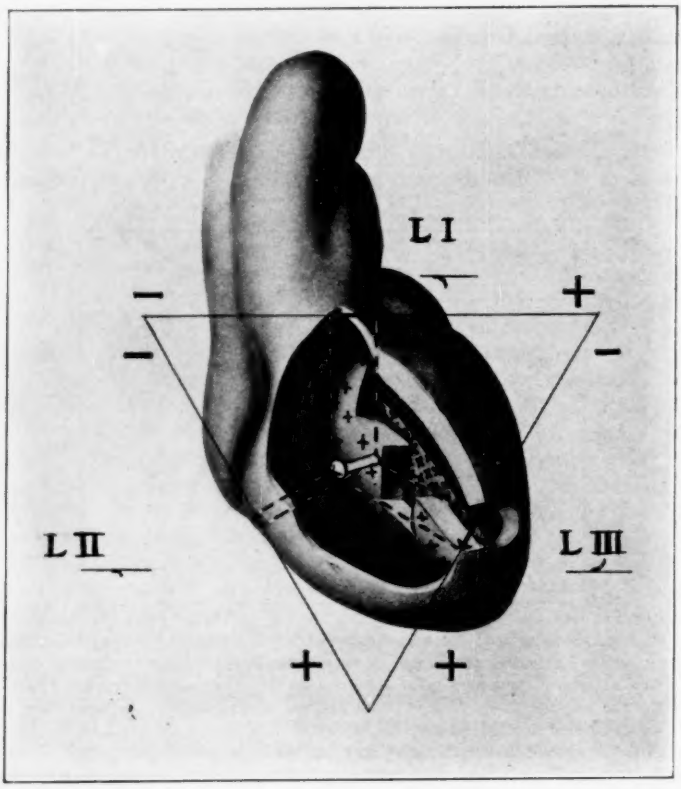

Fig. 2.—The heart viewed from directly in front. The anterior wall of the right ventricle is cut away, together with most of the anterior margin of the septum, and an opening is shown above the septum and at the apex into the left ventricular cavity. Many crosses are shown on the exposed left surface of the septum and few on the right surface to indicate that activation is farther advanced on the left surface. The Q vector is represented by the white arrow "emerging" from the septal wall.

Hence, the surfaces are represented not as being fully active but as active only at certain points. The number of points of activation on the left surface is shown to exceed the number on the right surface. In consequence, depolarization is

11. Mahaim, E., and Winston, M. R.: Researches on the Comparative Anatomy and the Experimental Pathology of the Superior Connections of Bundle His-Tawara, Cardiologia **5**:189, 1941.

slightly farther advanced on the left than on the right, and a vector (not quite so long as represented) appears, pointing across the septum from left to right. Following Bayley [12] and, in a general fashion, Lewis,[4] this vector can be assumed to produce the Q wave in lead I and lead II in a heart thus rotated; in lead III it initiates the R upstroke. With clockwise rotation of the heart, this vector is supposed to initiate Q_3, as will be illustrated later.

We do not insist on this mechanism of production of the Q wave. When Q_1 is present in right bundle branch block, it is not larger than the normal Q wave. If the Q wave is formed by the septum at all, left ventricular effects alone must rapidly

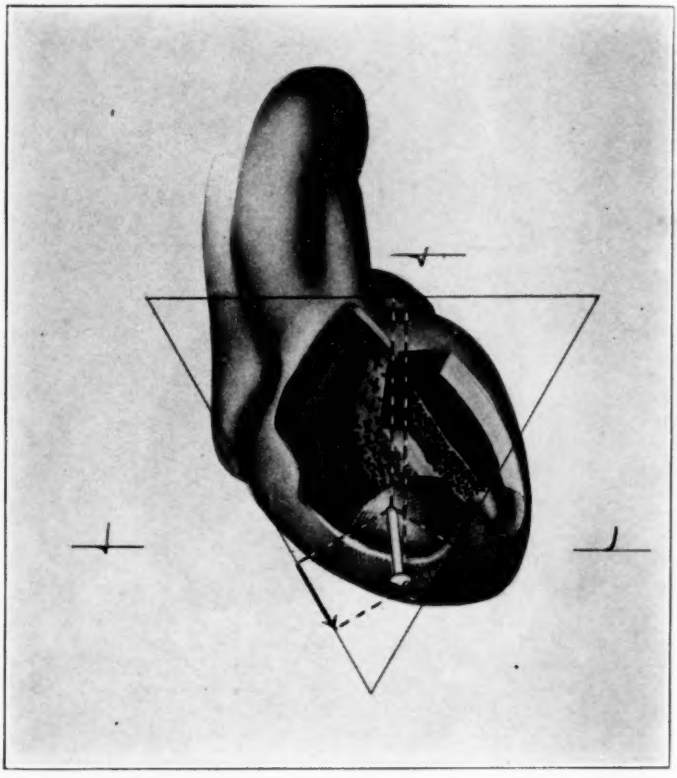

Fig. 3.—Activation has occurred about 0.01 second later than in figure 2. Complete polarized shells are shown on the endocardial surfaces of the ventricular apexes. The septum is approaching full activity on both sides (see text). The vector is the resultant of the two apical shells, that on the right being regarded as larger. It actually has a more forward direction than the picture appears to show. The right shell is larger than the left because impulses travel less far to reach the right, than the left, side of the apex.

produce a vector which opposes it and brings it to an end. On the other hand, as figure 3 shows, the next stage in activation of the subendocardial surfaces of the two ventricles is the formation of polarized shells within the ventricular apexes.

12. Bayley, R. H.: Theoretical Genesis of Q as Observed in the First Three Standard Leads of the Electrocardiogram: A Preliminary Report, J. Trop. Med. **41**:144, 1938.

Since right bundle branch block does not appreciably modify Q_1, it may be formed by the apical part of the septum and left ventricle, rather than, as Bayley has stated, by the anterior basal portion of the septal wall on the left side. Since Q_1 is typically abolished by left bundle branch block and not by block of the right branch, it is clearly a left-sided effect.

The foregoing conclusion fits fairly well the analysis reported by Hoff and Nahum for the dog's heart. It is probable from their experimental results, however, that Q_1 in the dog, although probably initiated subendocardially, is contributed to by some posterior portion of the cardiac wall after the impulse has penetrated

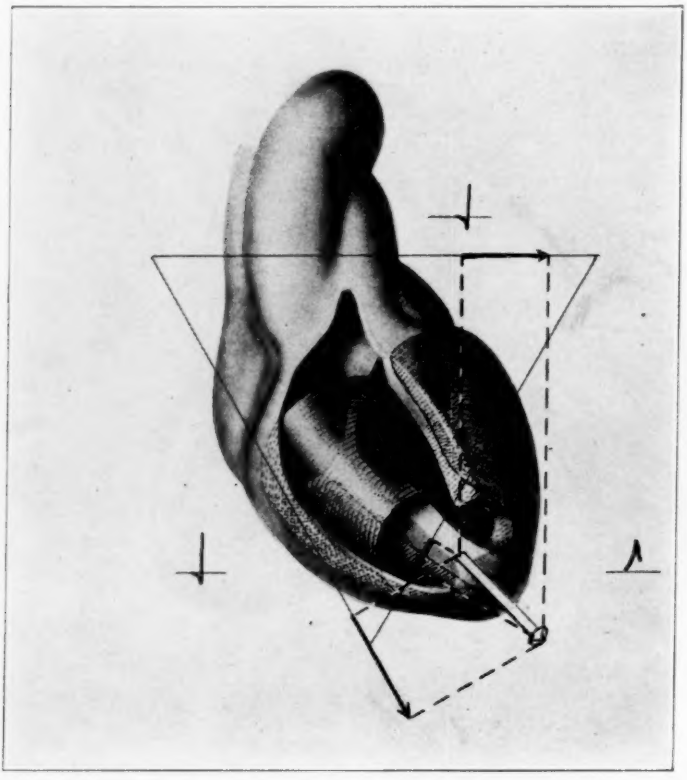

Fig. 4.—This stage shows that the impulses have broken through the ventricular walls anteriorly and apically. Elsewhere a large shell has formed in both ventricles, the endocardial activation of which is nearing completion. The vector is the resultant. This follows figure 2 after about 0.02 second. Septal shells are omitted in this figure because of difficulty of representation. In this figure and in the succeeding two figures the margin of the polarized shell of the left ventricle should have been shown extending to the epicardial surface except at the base.

the left ventricular apex. It is unlikely, because of the small size of Q_1 in most human records, that this often happens in man. In man the Q wave is typically initiated before impulses have penetrated the ventricular wall at any place.

Figure 3 follows figure 2 by about 0.01 second, but is about 0.015 second after the beginning of septal invasion. The septal polarized shells are now

practically complete (although shown as if somewhat incomplete), and shells have been formed within the ventricular apexes. The electrical effects of the shells on the two sides of the septum nearly balance each other. The two vectors, one for the right and one for the left ventricular apex, may be summated to give a single resultant vector which points downward, forward and slightly to the left when the heart is in this position. The Q wave has already been completed. The distribution of the electrical potential fields is such that R_1 has just begun, R_2 is well on its way upward and R_3, initiated by the Q effect, is rising sharply.

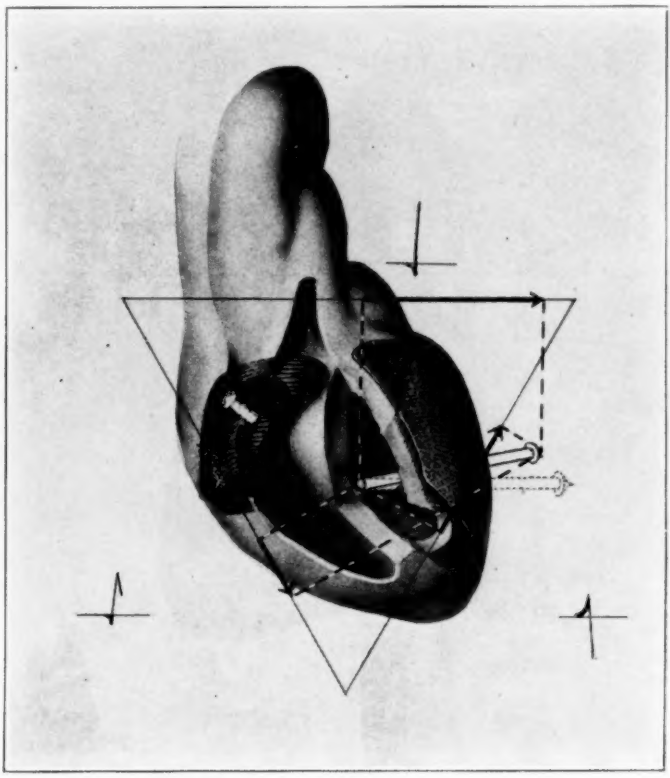

Fig. 5.—About 0.01 second after figure 4 and 0.04 second after the beginning of ventricular activation the shell has disappeared from most of the right ventricular wall and has slightly diminished in area in the left ventricle. The solid vector is the resultant. The vector now points somewhat backward, as well as to the left.

No further comment on this figure seems needed, except to note that in the dog, at least, even at the stage given, the impulses may already fully have penetrated the anterior ventricular walls near the septum, particularly on the right. In the dog, also, Q_1 may still be in progress at about this stage.

As Harris [6] demonstrated, confirming Lewis and Rothschild's [8] calculations, once the subendocardial spread of the impulses has begun, the progress is rapid. In figure 4, only 0.010 second later than figure 3 and 0.025 second after the impulse began to invade the septum, the excitation has traveled to involve the major part

of the subendocardial surface of the two ventricles. It has also penetrated to the subepicardial surface of the right ventricle, anteriorly, apically and upward for a distance near the septum, and less extensively the impulse has penetrated the wall just above the apex of the left ventricle. Active muscle, just like inactive muscle, is electrically inert. The polarized shells within the walls of the two ventricles are shown in the figure. The shells have openings, as already indicated at and near the apex, and they have not yet grown to involve the basal ventricular margins. The resultant of the electrical effects of the polarized shells is shown by the arrow which points downward, to the left and a little forward. The effect of this vector

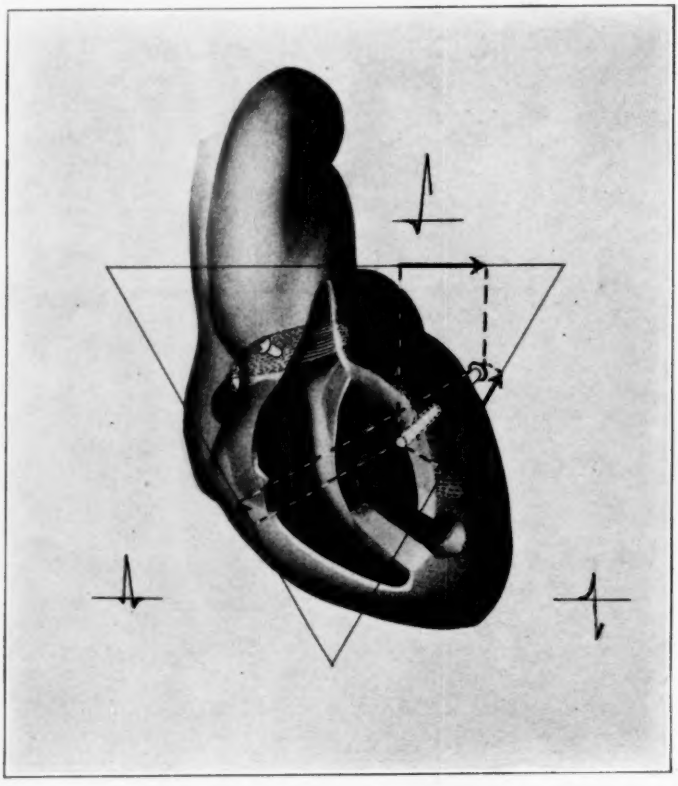

Fig. 6.—A still later stage, about 0.02 second after figure 5. The posterolateral left ventricular shell is dominant.

is also shown as projected on each lead. Thus, R_1 has climbed higher, and R_2 has risen less, while the downstroke of R_3 has begun, since this vector in the counterclockwise rotated heart points nearly at right angles to the line of lead III.

At this stage possible electrical effects from the interventricular septum may be neglected, since the two septal vectors, one on each side of the septum, are opposite in direction and counterbalance each other.

Figure 5 shows a still later stage, about 0.04 second after the beginning of the QRS complex. The thin-walled right ventricle is depolarized except for its basal margin and the region of the pulmonary conus. The relatively thin apical wall of

the left ventricle is also fully active, but a shell is still present in the lateral and basal walls, as shown. The shell in the right ventricle produces a vector, of moderate length, which points upward, forward and toward the right. The much larger shell in the left ventricle produces a vector which points almost directly to the left and somewhat backward. The vector resulting from the two is drawn in solid lines. It causes R_1 to reach its apex. Meanwhile R_2 is descending, and S_3 is already far on its downstroke. As we shall show later, a clockwise rotated heart may not show an S_3; our description applies to the rotation shown in the figure. We may say here that moderately deep S_3 waves and so-called "left axis deviation" are not

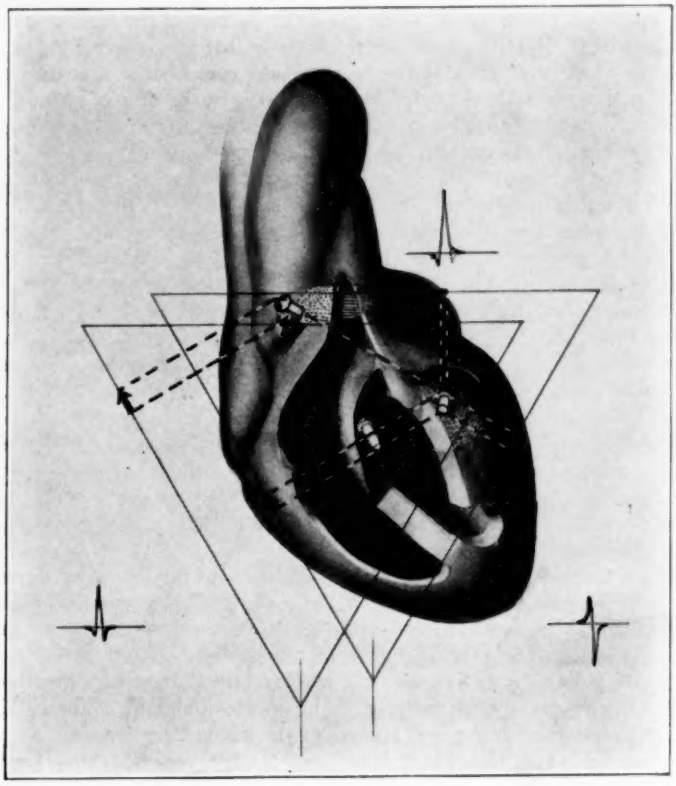

Fig. 7.—Nearly the whole ventricular musculature has become active. The vector in the conus is shown projected on one triangle. The left ventricular vector is projected on the other. The small central arrow is their resultant. At this stage one or the other vector may have disappeared. If the left ventricular vector vanishes first, an S wave appears in lead I; if the conus vector vanishes first, there is no S wave in lead I. The QRS complex is completed, as shown, in less than 0.01 second after this stage. The deflections on all figures in this paper are drawn to scale (3:1).

unusual in persons of sthenic build, whose hearts are placed in an average position with reference to rotation around an anteroposterior axis.

Figure 6 shows a still later stage, about 0.02 second after figure 5. The two vectors summate to give the vector shown for the left ventricle. Thus, R_1 is descending; S_2 is being formed, and S_3 is on its ascending limb.

The stage shown in figure 7 is the last one to be represented. Here, the right ventricular vector (now limited to the pulmonary conus) and the left ventricular vector in the basal, posterolateral left ventricular wall are separately projected on the lines of the leads. The central arrow is their resultant. In the dog the conus region is often, and perhaps usually, the last to be activated, but Harris found the base of the left ventricle to be just as late in the monkey. Very likely there are individual variations in lateness, both in human beings and in animals, and certainly there is considerable variation in the terminal parts of the QRS in human beings. If the left ventricular vector is last in figure 7, no S_1 will appear. If the conus is equally late, or later, there will be an S_1. Hoff and Nahum attribute S_3 to the anterior surface of the right ventricle after activation of the posterior surface of the left ventricle. The results of Lewis, of Harris and of others all show that the anterior surface of the right ventricle in question must be the region of the conus, since it is the only right ventricular region not fully activated at the time S_3 in the dog is formed. In the dog, the heart of which is not rotated as in our figures, the conus, therefore, almost certainly contributes to S_3 and may alone be responsible for it, though other regions have not rigorously been ruled out. In man, depending on the position of the heart, the conus may contribute to S_1 or to S_3 or to both. It may be added that a precordial lead from over the region of the conus in man usually shows a QRS complex with a terminal, upright (positive) deflection. This deflection is most plausibly to be ascribed to activity of the conus. Electrical exploration of the chest in this region may help elucidate the frequency and degree of conus contribution to the QRS complex in man.

As the vectors of figure 7 die away, the QRS complex becomes complete. The several vectors we have drawn represent stages in the development of the vectorcardiogram, which was mentioned in the introduction.

If the wall of the right ventricle were thoroughly warmed, the effect would be considerably to increase the velocity of the impulses, so that, for example, the shell shown in figure 4 would be stripped away early at a time when the vector produced by the left ventricle is near its maximum magnitude. The effect would be greatly to increase the height of the R wave. This has, in fact, been accomplished by Nahum, Hoff and Kaufman,[7a] in the dog in a beautiful series of experiments. Conversely, cooling the right ventricle will cause the shell to persist so long that full activation of muscle of the left ventricular wall occurs before full activation of the right wall. Consequently, the R vector of the left wall is almost fully counterbalanced by the persisting shell in the right wall, and the R waves are greatly reduced in height. Analogous, though reverse, results were found by Nahum, Hoff and Kaufman [7a] to follow warming and cooling of the left ventricular wall.

In an earlier paper Kisch, Nahum and Hoff [13] reported that injection of potassium chloride solution into a ventricular wall had little or no effect on the electrocardiogram. In contrast, when the solution was applied to a small epicardial region, deviations of the RS-T segment appeared. The authors, therefore, concluded that the electrical variations recorded by the electrocardiograph were produced exclusively, or almost exclusively, on or by the epicardial surface. No such conclusion is justified, since the intramural injection of potassium chloride solution produced depolarization of a region of muscle surrounded on all sides by normal muscle and the electrical forces are fully counterbalanced, in much the same way that the left ventricular vector producing R_1, for example, is partly counterbalanced or offset by the vector simultaneously present in the right ventricle.

13. Kisch, B.; Nahum, L. H., and Hoff, H. E.: The Predominance of Surface over Deep Cardiac Injury in Producing Changes in the Electrocardiogram, Am. Heart J. **20**:174, 1940.

Our conception of the mechanism of production of the QRS complex is not new. Aside from details, it is the type of explanation advanced by Lewis and by many subsequent investigators. So far as we know, however, this is the first attempt to present the explanation in some detail. As further evidence, aside from the obvious implications of the experiments quoted, we refer the reader to figure 8, an electrocardiogram of the type described, obtained on a healthy male subject aged 23. The form of the QRS complex in each lead and the relative times of inscription of the various peaks are especially to be noted and compared wth the QRS complexes of figure 7. There is a notching of R_3 in this case, which is not accounted for by our vectors. A similar notch is not uncommon in records of this type, and it may be ascribed to an abrupt shift in vector direction between vector 3 and vector 4, probably caused by normal irregularities in the growth and decline of the right

Fig. 8.—An electrocardiogram made on a normal, recumbent, medical student aged 23. The QRS complex is discussed in the text. In lead I, and less successfully in the other leads, the heart was "voluntarily" accelerated. It is worth noting that the Q-T interval did not at once fall to the duration "normal" for the heart rate in lead I. This case is further discussed by Ashman and Byer.[15]

and the left ventricular vectors which summate to give vectors 2, 3 and 4. Phenomena of this sort, which are also responsible for the frequently seen splintering of low QRS complexes in lead III, will usually be visible only on waves of low amplitude and are, no doubt, subject to individual variation. Obviously, these minor, more or less individual peculiarities cannot be considered in any schema as simple as the one we present. Returning to the subject of figure 8, there is, unfortunately, no way to be certain that his heart is, in fact, rotated counterclockwise on its long axis since this cannot be determined fluoroscopically. In support of our assumption that records similar to figure 8 indicate that the heart is rotated counterclockwise on its long axis, as compared with the average position of the heart,

we may refer to the old observations of Meek and Wilson.[14] They found that rotation of the dog's heart on its long axis produced changes in Q and S waves similar to those we have pictured for man. Aside from these experimental observations, it is known that dilatation of the right ventricle, which usually leads to clockwise cardiac rotation, often causes a deepening of S_1 and of Q_3, whereas the reverse effects are commonly produced by left ventricular hypertrophy. And it is also a matter of common observation that in early infancy, when the right ventricular wall is nearly as thick as the left one, the electrocardiogram is of the type ascribed to marked clockwise rotation in the adult.

THE ELECTROCARDIOGRAPHIC EFFECTS OF CARDIAC ROTATION ABOUT THE ANTEROPOSTERIOR AND THE LONGITUDINAL AXIS

In the previous section we have traced the electrocardiographic consequences of the spread of the excitation wave through the ventricular muscle. To render the diagrams clearer, we chose a rather extreme position of counterclockwise rotation of the heart on its long anatomic axis as viewed from the apex. We shall now proceed to an examination of the effects produced by rotation of the heart to other positions about the anteroposterior and the longitudinal anatomic axis. A further word will be said at the end of this section about the effects of cardiac rotation about a transverse axis. Although different thoracic forms and cardiac positions may modify to some extent the diastolic shape of the ventricles, the electrical effect is apparently slight, and we have not attempted to take such influences into account. Needless to say, a change in intrathoracic cardiac position cannot be supposed to influence the sequence of ventricular activation.

Figure 9 illustrates the electrical effects of rotation of the counterclockwise rotated heart about its anteroposterior axis. Figure 9 *A* recapitulates in one figure the series of stages of activation which have already been described in connection with figures 2 through 7. The successive vectors at the six chosen stages of the previous section are numbered in sequence and are represented as if radiating from a common origin. The dotted line, beginning at the origin and connecting the tips of the arrows representing the vectors, is the approximate vectorcardiogram which would be recorded from this heart. It may be repeated that the ventricular vectorcardiogram is produced by the continuous series of instantaneous electrical axes which inscribe the ventricular electrocardiogram, and of this infinite series, we have chosen just six stages as representative.

Since the stages of activation shown in figure 9 *A* were described in the previous section, we may turn to figure 9 *B*, which shows the same heart, with the same degree of counterclockwise rotation about its long axis, after it is rotated about its anteroposterior axis to a more transverse position. It is evident that if the rotation is confined to the single axis, the effect will be simply a tilting upward of the vectorcardiogram toward the left shoulder and equal rotation counterclockwise of all the vectors about the anteroposterior axis. The electrocardiographic effects of this rotation, as compared to figure 9 *A*, are mainly to reduce the amplitude of R_2 and R_3 and to deepen S_2 and S_3. At the same time Q_1 may be reduced and Q_2 abolished, although, as stated previously, the true Q wave is less consistent than the other deflections.

Our own fluoroscopic and roentgen observations have shown hearts in sthenic persons, the silhouettes of which were similar to that of figure 9 *A*, which yielded

14. Meek, W. J., and Wilson, A.: The Effect of Changes in the Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. **36**:614 (Nov.) 1925.

similar electrocardiograms. It is, of course, generally known that transversely placed hearts are likely to produce records similar to that of figure 9 *B*. It has been stated that supposed discrepancies, namely, hearts in an average position (as fig. 9 *A*) yet showing a "left axis deviation," demonstrate the inutility of vector analysis. On the contrary, the signs of rotation revealed by the electrocardiogram are often useful, since they may reveal rotations due to pathologic conditions, some of which may be transient, as in massive pulmonary embolism.

Figure 9 *C* shows the same counterclockwise rotated heart, rotated in a clockwise direction about the anteroposterior axis. Such a combination of rotations is

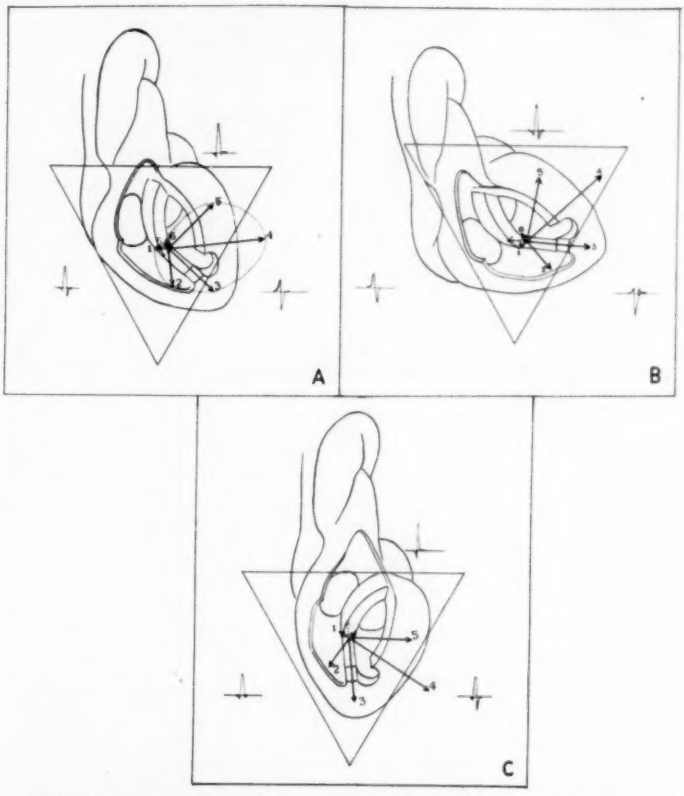

Fig. 9.—See text for explanation. Note that S_1 and the similarly timed wave in lead III show two alternative amplitudes.

unusual under normal conditions in the human heart but may occur in some cases of hypertrophy of the left ventricle. The electrocardiogram, compared with that of figure 9 *A*, shows a Q wave in all leads, an augmentation in the height of R_3 and some decrease in R_1, together with shallower S_2 and S_3.

We may now turn to the evidently more common condition, namely, slight counterclockwise rotation from the "average" position about the longitudinal axis. The "sthenic" position of such a heart is shown in figure 10 *A*. In contrast to the more strongly rotated heart, S_3 is less deep and S_2 may be absent. Other changes are slight. It may be observed, however, that vector 6, which produced a small

S_1 in figure 9 *A*, may here be directed almost straight backward, producing practically no effect. As we have pointed out, since the smaller S waves may be produced either by the conus or by the posterior, basal, left ventricular wall or by both, depending on the relative times of full activation of these regions, variability in small S waves is to be expected. Such variability is actually observed. S_3 in figure 9 *A*, on the other hand, is a posterolateral left ventricular effect, produced in the region which contributes to R_1, and is not subject to variation in the same way.

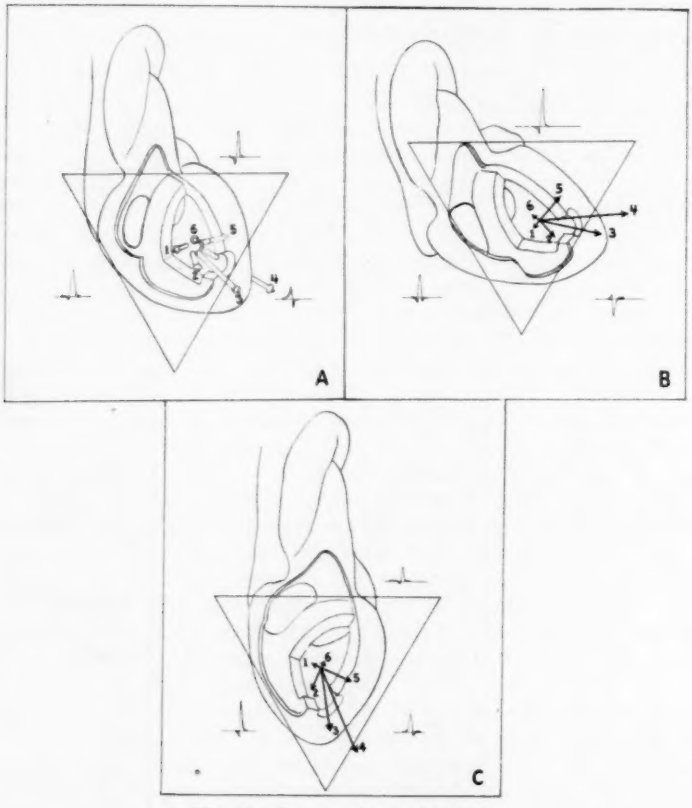

Fig. 10.—See text for explanation.

Figures 10 *B* and *C* illustrate, respectively, the effects of rotation to a more transverse and to a more vertical position. The transversely rotated heart shows a deeper S_3 and a low R_3, and S_2 is likely to be present. R_1 is higher. The other changes from the "sthenic" position are unimportant. The vertical heart (fig. 10 *C*) reveals a higher R_3 and a less deep S_3, together with a much lower R_1. This record is not common.

Figure 11 shows a series of hearts which are rotated slightly in a clockwise direction from the "average" about the longitudinal axis. Probably more human hearts fall into this group than into any other single one, though it must also be stated that vertical hearts, in particular, show this type of record, whereas trans-

verse hearts are more likely to show some degree of counterclockwise rotation. In contrast to the previous series of rotations, the vectorcardiogram, emerging from the origin, circles now to the left and then to the right and upward, to regain the origin with disappearance of S_1. We now find in figure 11 *A* that Q_1 is absent and Q_3 is present. R_1 and R_3 are of nearly the same height. S_1 is present, and S_3, unless contributed by late activity of the conus, is absent.

When this heart is rotated to a transverse position, as in figure 11 *B*, R_1 becomes higher and R_3 lower. Q_3 becomes prominent. This electrocardiogram

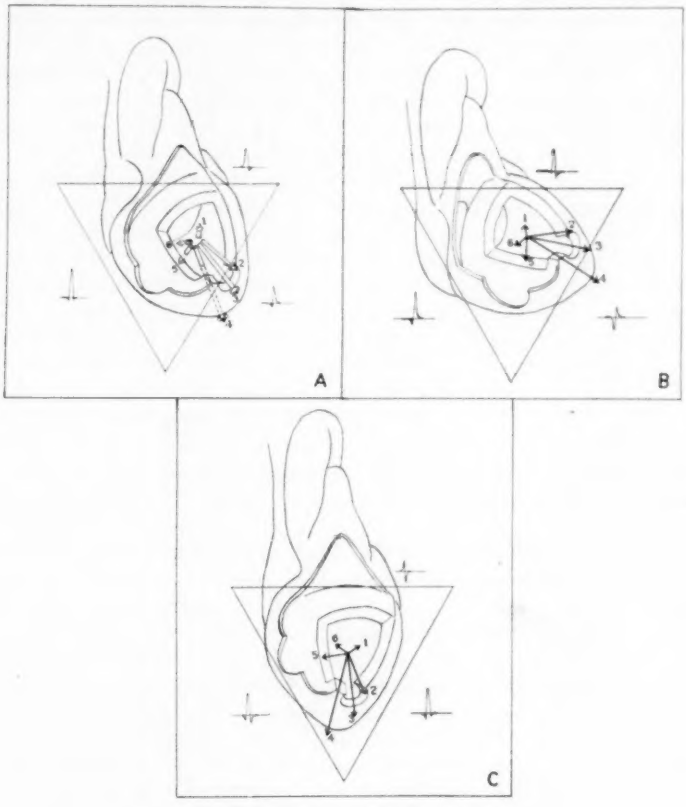

Fig. 11.—See text for explanation.

occurs fairly commonly in obese persons, particularly women perhaps, and in pregnant women. In these persons the electrocardiogram is presumably often made from a heart of the figure 11 *A* type pushed toward or to the figure 11 *B* position.

Another, commoner, picture is that of figure 11 *C*. It is characteristic of tall, slender persons. R_1 is low; R_2 and R_3 are relatively high. S_1 is present, and there are often S_2 and an S_3, depending on the relative contributions from the posterior, basal, left ventricular wall and the pulmonary conus.

We finally come to the series of figure 12. The heart is here rotated strongly in a clockwise direction, as viewed from the apex. In the "sthenic" position (fig.

12 *A*), except for the depth of S_1, the picture differs but little from that of figure 11 *A*. The strongly rotated vertical heart (fig. 12 *C*) shows a relatively high R_3.

Although the electrocardiograms of figure 12 are encountered in some normal persons, they have a special bearing on the changes which appear in association with massive pulmonary embolism or other conditions associated with dilatation of the right ventricle. Obviously, patients whose hearts are in any position of rotation may fall victim to pulmonary embolism. If the antecedent position was one of considerable counterclockwise rotation (fig. 9), only a great degree of dilatation of

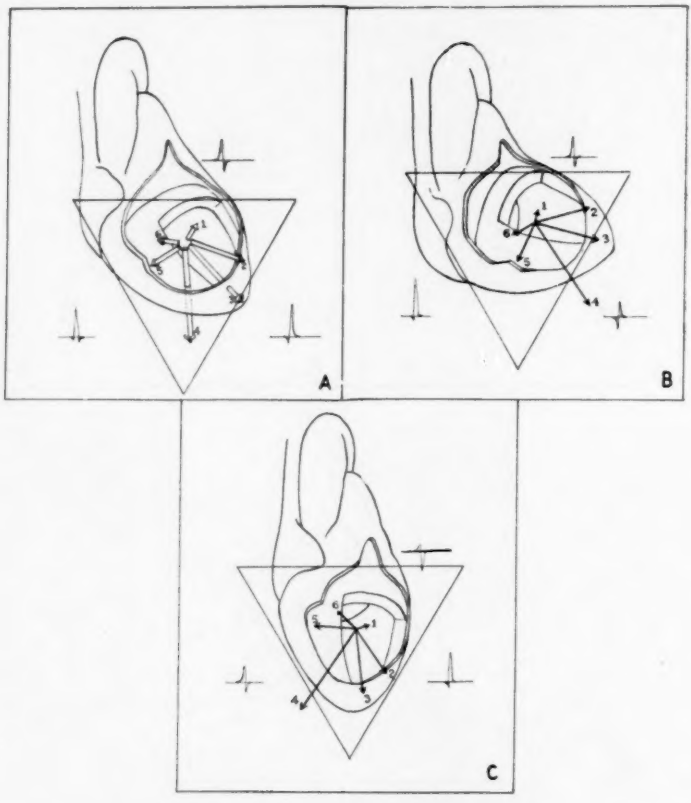

Fig. 12.—See text for explanation.

the right ventricle could produce the picture of figure 12, whereas much less dilatation could rotate the heart of figure 11 to this more extreme position. Undoubtedly, this is one of the factors which prevents the development of the characteristic electrocardiogram in cases of pulmonary embolism. Dilatation of the left ventricle appears to be capable of producing relatively little rotation of the heart about the long axis, since the ventricle is free to bulge backward.

The rotations which have been described, both in normal conditions and in conditions which lead to dilatation of the right ventricle, are associated with consistent rotations of the ventricular gradient, resulting in characteristic changes in

the T wave. These have been described in part by Ashman and Byer.[15] A paper to be published [16] shows the cardiac silhouettes of a number of subjects. Almost without exception, we could have predicted the intrathoracic position of these hearts from the electrocardiogram alone.

EFFECT OF CARDIAC ROTATION ABOUT THE TRANSVERSE AXIS

The foregoing analysis takes account of electrocardiographic variations resulting from rotation about only two of the three possible axes of rotation, namely, the longitudinal and the anteroposterior. It is evident that in some persons the heart must be relatively vertical, for example, not only with reference to rotation about the anteroposterior axis but with reference to rotation about a transverse axis. Such a person would have a narrow anteroposterior thoracic diameter, as a rule, and would possess a truly so-called "dropped heart." The electrocardiographic effects may be inferred from figure 11 *C*, which shows a heart rotated slightly clockwise and vertically with respect to the anteroposterior axis. If the apex of such a heart were pushed back or the base pulled forward, vector 1, which points forward and slightly to the left and upward, would point slightly to the left and downward. Consequently no Q wave would appear in any lead, the Q effect now appearing as the beginning of the R waves. This essentially follows the analysis of the Q wave as given by Bayley.[12] At the same time vectors 2 and 3 would point more directly downward, and this would accelerate the upstroke of R_2 and R_3. Vector 4 points downward, to the right and backward. The rotation will cause it to become shorter, as projected on the frontal plane, so that R_3 will be reduced in height, unless the shortening of vector 4 is compensated for by the lengthening of vector 3. Vectors 5 and 6 will point more nearly directly upward than they do in the figure, and this will deepen the S wave in all three leads. Such electrocardiograms, displaying little or no Q wave, a rather low R_1, a higher R_2 and a well marked S wave in all three leads, are by no means uncommon. In many instances, at least, they are associated with the postulated body build.

Some electrocardiograms of the type described in the previous paragraph show relatively low R waves in all leads. This cannot be explained on the basis of our diagrams, but it is quite consistent with the experimental findings of Harris.[6] It may be recalled that the wave of excitation reached the anteroapical epicardial surface of one of Harris' monkeys somewhat earlier than in the other. If this early penetration of the walls means that epicardial activation occurs before the shells producing vectors 2 and 3 have expanded within the ventricular wall, then these vectors will be distinctly shorter than they are represented in our diagrams. When such a heart is "dropped" the R waves will be relatively low. As a matter of fact, the observations of Ashman and Byer [15] and the experimental results of Hoff and Nahum obtained on the dog suggest that our vectors 2 and 3 are, in fact, relatively a little longer than they are in reality in many human hearts. We arrived at this conclusion only after our figures were drawn. Had the vectors been made shorter, the effects would be slight except in a few cases, particularly in the case of the "dropped" heart.

A second, fairly large, class of electrocardiograms is similar to those of figures 11 *A* and *C* and 12 *A* and *C*, but no S wave is present in lead II and R_2 and R_3 are relatively higher. This is the picture which would be produced by pulling the apex slightly forward or pushing the base backward. Vector 4 is lengthened by

15. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient: I. and II., Am. Heart J. **25**:16 and 36, 1943.

16. Ashman, R.; Gardberg, M., and Byer, E.: To be published.

this rotation about the transverse axis; vector 5 may point more toward the galvanometer electrode on the left leg than toward that on the right arm, and vector 6 points nearly at right angles with the line of lead II. In a few instances we have been able to observe that subjects whose records are of this type are distinctly deeper chested than those with "dropped" hearts. Extensive future correlation is needed, however, before we can assert that the suggested differences are generally consistent.

A third type of electrocardiogram is illustrated by our series only as an alternative form in figure 9 *B* and shows a W complex in lead I, namely a distinct Q_1, an R_1 which may be high and a distinct, but not deep, S_1. In lead III there are a low R wave, an S wave, the depth of which is variable, and a final upright deflection (M complex). When S_3 is more than 2 or 3 mm. deep, at least, a comparison of the QRS axis and the ventricular gradient indicates that the heart is rotated more or less counterclockwise. This may represent a heart of the type shown in figure 10 *A* or *B* or 9 *A* or *B* but with the apex farther forward or the base farther back. Vector 5 and the pulmonary conus could still write an S_3, but vector 6, now pointing downward and to the right, being produced by late activation of the conus, could give a final S wave in lead I and a final upward deflection after the inscription of S_3. We have not been able to confirm this suggestion, which at best might be difficult to prove by fluoroscopic or other evidence.

Only one other fairly common type of electrocardiogram remains, which is not covered by our series. It is the type showing a Q wave in all three leads and no S wave. Such a picture will result if the base of a nonrotated heart is tilted backward.

Our diagrams also fail to illustrate an intermediate type, with no rotation on the long axis, namely, what we call the average position of rotation for want of a better term. At this position the plane in which the vectors lie will be seen edgewise. If the heart is slightly transverse, the larger vectors, namely, vectors 2, 3, 4 and 5, may have a direction at right angles to the line of lead III. Under these circumstances, a slight deviation of the vectors, one out of the common plane to one side, another a little bit to the other side, etc., will produce a splintering of a low QRS_3. This is, of course, a perfectly normal phenomenon, as every electrocardiographer knows.

COMMENT

In a paper by Ashman and Byer,[15] which studies the relation between the QRS complex and the ventricular gradient, the conclusion is reached that the mean, or average, electrical axis of the QRS complex in a few normal hearts may point directly backward or even backward and slightly upward. This conclusion would have seemed incredible to us, had it not been for the results of the present study. It will be noted, however, that vectors between 2 and 3 in our figures point relatively forward for about 0.02 second, whereas vectors between 4 and 5 point relatively backward for at least 0.03 second. Furthermore, the average length of the vectors between 4 and 5 in three dimensional space is at least double the average length of vectors between 2 and 3. Hence, since the larger vectors point relatively backward for a longer time, and the shorter vectors point relatively forward for a shorter time, the mean electrical axis of the QRS complex will point relatively backward, that is, backward, downward and usually to the left. But in some "dropped" hearts, particularly when anterior subepicardial activation is relatively early, the mean QRS axis may point straight backward at right angles to the frontal plane or even backward and upward. When the mean axis is indicated on a good model of a heart and the heart is placed in a vertical position, this is easy

to visualize. In support of this conclusion is the picture often seen after anterolateral infarction, which has eliminated much of the left ventricular muscle which normally contributes to vectors 2 and 3. QRS_1 is low, often with a deep Q wave; R_2 and R_3 are low, and there are a deep S_2 and S_3. The mean electrical axis under such circumstances points backward and upward, its upward direction being greater than in any normal hearts. We have observed axes which point backward and slightly upward in conditions, such as bronchial asthma, which, by one mechanism or another, render the heart more vertical. We do not intend to deny by this analysis, however, that some distortion of the electrical fields by the thoracic configuration and by the lungs may not contribute a little to the relatively backward direction of the mean QRS axis. We do believe that such factors are of secondary importance.

Finally, we may inquire into the bearing our analysis has on the moot question of the validity of the Einthoven triangle method of determining the directions of the electrical axes. It may be pointed out again that we exercised considerable care in fixing the orientation relative to each other of the ventricular walls and their relative thickness in different regions. From roentgenograms the range of variation with respect to the anteroposterior axis is well known. The degrees of rotation around the longitudinal axis cannot be directly determined from a roentgenogram, and the amount of rotation is largely inferential. Our clockwise and counterclockwise rotations probably represent the extremes under normal conditions. The vectors have been drawn in accordance with the best evidence from investigations on animals and human beings, and their approximate correctness is supported by the comparison of the QRS axis and the ventricular gradient. It is, of course, impossible to be sure that the various rotations suggested by the electrocardiogram of any subject are actually present. Nevertheless, the correspondence between the constructed electrocardiograms and those actually observed is close. It is so close, in fact, that the presumption is strong that the direction of a vector as recorded is nearly its true direction in a large majority of persons. Wilson and Johnston [1] were evidently of the same opinion. It may be recalled that there are 360 degrees in a circle. Even if the recorded direction of a vector is often in error by $\pm$ 10 degrees, which seems to be a reasonable limit of error, this 20 degree range is only 11.2 per cent of a half circle, as small an error as is found in other determinations or measurements of admitted usefulness in medicine. Even if there were no error (which is impossible except as a rare coincidence), the absolute direction of the axis is of far less importance than the comparison between the direction of one vector, for example, the mean QRS axis, and of another vector, such as the ventricular gradient. It is reasonably certain that the error which affects the one will affect the other almost equally and in the same sense. In this case it becomes irrelevant whether the directions indicated are quite accurate. It has been stated that the fact that a patient's elecrocardiogram often fails to reveal a left axis deviation in the presence of left ventricular hypertrophy proves that vector analysis is invalid. On the contrary, vector analysis, with roentgen support, has shown that not all patients with left ventricular hypertrophy should show left axis deviation, and the analysis has enabled us much more accurately to recognize the hypertrophy in the absence of the deviation. This will be considered in a later paper.

It is, of course, true that there are certain conditions in which the direction of the vector as determined cannot safely be regarded as its approximately true direction. These conditions include some cases of pulmonary disease, pleural effusions, pneumothorax, extreme scoliosis or kyphosis and possibly adhesive peri-

carditis. In bronchial asthma during an attack, during deep inspiration by a normal subject and possibly in pericardial effusion, the error may be magnified. The presence of fluid in the thorax or abdomen will reduce the magnitude of the vectors. However, the changes produced by respiration, as illustrated, for example, in Master's [17] useful book, can be fully explained on the basis of the changes in cardiac position.

SUMMARY

An analysis is presented of the QRS complex of the human electrocardiogram and of the variations in that complex which should appear when the heart is rotated to different positions within the thorax. Among different subjects there are considerable differences in the cardiac position within the thorax, and the effects of these differences are explained. In making the analysis we have correlated (1) experimental findings in the experimental animal; (2) known effects of rotations of the heart in man produced by normal procedures or certain pathologic conditions; (3) known effects of bundle branch block and of infarction in man, and (4) information derived from studies of precordial leads. Less attention was given to the conflicting anatomic studies of the Purkinje system. In order to visualize the electrical events in three dimensional space, clay models have been used.

The reader must judge for himself how successful the analysis has been. We are convinced that in a large majority of subjects the directions of the electrical axes as revealed by the limb leads and as projected on the frontal plane are correct within ± 10 degrees, and the usual error may be less than this. It is pointed out that even if the error should be greater, the value of vector analysis is not thereby impaired in its more important applications.

Mr. W. B. Stewart, of the art department of the School of Medicine, made the figures illustrating this paper.

17. Master, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942.

PHYSICAL THERAPY APPLIED AT HOME FOR ARTHRITIS

A FOLLOW-UP STUDY, WITH A SUPPLEMENTARY SUMMARY OF THE SEDIMENTATION RATE OF ERYTHROCYTES IN TWO HUNDRED AND TWENTY-NINE CASES OF ARTHRITIS

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In the general therapeutic program outlined for the patient who has arthritis physical therapy has come to play one of the central roles. The physical therapeutic measures, considering the usual chronicity of the types of arthritis treated, must be applied persistently and patiently over a long period. It can be fairly stated that most likely in every case of chronic arthritis home treatment with physical measures finds a place, either as a less elaborate continuation of the beneficial measures carried out in a physical therapy department by trained personnel or as a primary home regimen of simple physical measures. Because of the chronicity of the more common types of arthritis and because the average patient with the chronic form of arthritis is unable financially to continue with indefinite institutional treatment, an organized plan was developed at the Mayo Clinic for encouraging arthritic patients to carry out simple physical therapeutic measures in the home under the supervision of physicians in their home localities. The three main groups of physical measures employed are (1) thermal measures, including heat, cold and contrast baths; (2) massage and manipulation, and (3) exercise, including general postural training. The specific physical procedures advised for application at home, as adapted to the individual case and to the varying home facilities, have been considered in detail in previous articles.[1]

Many and varied are the ways of utilizing each of these three groups of essential measures, and it is important that the arthritis in each case be considered from the standpoint of causation, type, severity, duration, joints involved and expected results and then individualized treatment be planned, if real and lasting benefit is to be expected from physical therapy. For several years a plan has been in effect at the clinic whereby every arthritic patient seen by a physician in the Section on Physical Therapy is prescribed for individually and is given a minimum of one instructional treatment by a trained technician. The patient is instructed during this demonstration treatment in just how he is to carry on treatment at home. A few additional instructional treatments are recommended when this fits in with the patient's temporal and financial economy; in addition, on dismissal, each patient

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1. (*a*) Hench, P. S.: Chronic Arthritis, in Barr, D. P.: Modern Medical Therapy in General Practice, Baltimore, Williams & Wilkins Company, 1940, vol. 3, pp. 3298-3397. (*b*) Hench, P. S.; Bauer, W.; Boland, E.; Dawson, M. H.; Freyberg, R. H.; Holbrook, W. P.; Key, J. A.; Lockie, L. M., and McEwen, C.: Rheumatism and Arthritis: Review of the American and English Literature for 1940 (Eighth Rheumatism Review), Ann. Int. Med. **15**:1002-1108 (Dec.) 1941. (*c*) Krusen, F. H.: Physical Therapy in Arthritis, with Special Reference to Home Treatment, J. A. M. A. **115**:605-615 (Aug. 24) 1940; (*d*) Physical Therapy in Arthritis, New York, Paul B. Hoeber, Inc., 1937.

is given detailed exact written instructions. In other words, physical therapy is prescribed as individually and specifically as any other medical or therapeutic measure.

It is recommended that whenever possible patients should have professional physical therapy twice a week to supplement and further guide the home routine. In the majority of cases, however, facilities for these regular weekly or twice weekly additional treatments by a skilled technician are not easily available.

We realize the obvious difficulty of evaluating any treatment for chronic arthritis, especially when such treatment is only one part of a complete well planned program of general treatment which the patient is advised to carry out under the general supervision of his physician. Nevertheless, from the purely practical standpoint we felt it would be interesting and valuable to know whether the patients were carrying out their prescribed treatments and for how long. Also, we wanted to know whether the patients themselves believed that the physical treatments were helping them. After all, it is important to know if the patients think the treatment is beneficial. This does not prove that it is, but it does indicate in a sense whether it is worth while to continue prescribing it.

In order to answer these questions a follow-up study was carried out, which proved interesting to us.

TABLE 1.—*Types of Arthritis*

Type	No. of Cases	Percentage of Cases
Rheumatoid arthritis	97	44.5
Osteoarthritis	84	38.5
Periarthritis of shoulder	17	7.8
Traumatic arthritis	3	1.4
Psoriatic arthritis	3	1.4
Arthritis of questionable type	3	1.4
Total	207	
Cases not used in detailed analyses	11	5.0
Total	218	100.0

ANALYSIS OF DATA

The 346 cases analyzed in the follow-up study were taken at random from a group of several thousand cases encountered during 1940. In each case, a diagnosis of arthritis of some type had been made as one of the major diagnoses and the patient had been seen in consultation in the Section on Physical Therapy. Follow-up data, in response to a questionnaire, have been obtained in 218 of the 346 cases.

The simple distribution of the types of arthritis in this group of 218 cases is given in table 1. There were 97 cases (44.5 per cent) of rheumatoid arthritis in all stages and 84 cases (38.5 per cent) of osteoarthritis in this group. In some cases of the latter disease secondary fibrositis was associated, but the primary difficulty was considered by the clinician in each case to be osteoarthritis. In 3 cases the type of arthritis could not be ascertained definitely. Eleven cases were not used in the detailed analysis of the results in the various types of arthritis for miscellaneous reasons, such as uncertainty as to diagnosis, unrelated coincident illness which complicated the condition, the use of unorthodox treatments in addition to the recommended treatment and the carrying out of the treatment in a definitely unrecommended manner.

The number of cases in which patients carried out the whole treatment recommended or a significant part of it for various intervals of time is given in table 2.

Since the study was made of cases encountered in 1940 and since the questionnaires were sent out in December 1941 and January 1942, a patient could have carried out the treatment for a maximal period of one to two years.

Of the whole group of 218 cases studied, in only 16 (7.3 per cent) was the home treatment not carried out at all. This included cases in which patients did take some physical therapy but for various reasons did not follow the recommended home treatment. It is seen further that in about two thirds of the cases the treatment was carried out for three months or longer, and in more than a fourth of them the patients were still doing at least part of the treatment one year or more after leaving the clinic. On the questionnaire the patient was asked merely, "Do you think you were benefited by the home treatment? Please describe briefly." Benefit

TABLE 2.—*Length of Time Treatment Was Continued at Home*

No. of Months	No. of Cases	Percentage of Cases
0-2	61	28.0
3-5	32	14.7 64.7
6-11	51	23.4
12 or more	58	26.6
No home treatment	16	7.3
Total	218	100.0

TABLE 3.—*Subjective Evaluation of Benefit from Treatment at Home*

Type of Arthritis	Grade of Benefit +3	+2	+1	0	−1	No Home Treatment, No. of Cases	Total No. of Cases
Rheumatoid arthritis	42 (43.3%)	27 (27.8%)	16 (16.5%)	12 (12.4%)	0	0	97 (100%)
Osteoarthritis	33 (39.3%)	20 (23.8%)	7 (8.3%)	10 (11.9%)	3 (3.6%)	11 (13.1%)	84 (100%)
Periarthritis of shoulder	8	4	5	0	0	0	17
Traumatic arthritis	1	1	0	1	0	0	3
Psoriatic arthritis	3	0	0	0	0	0	3
Arthritis of questionable type	0	3	0	0	0	0	3
Cases not used in detailed analysis	1	0	3	2	0	5	11
Total	88	55	31	25	3	16	218
Percentage	40.4	25.2	14.2	11.5	1.4	7.3	100
		79.8			20.2		

was graded as follows: An enthusiastically favorable reply, more than just "yes," was graded plus 3; a simple unqualified "yes" in answer to the question was graded plus 2; "yes" with qualifications was graded plus 1; no benefit, no harm or a simple "no" was graded 0, and the reply "Harmed by the treatment" was graded minus 1. A detailed analysis of the patients' subjective evaluation of the treatment is given in table 3.

Of all cases, the patients in 3 (1.4 per cent) thought they were harmed by the treatment, the patients in 25 (11.5 per cent) carried out the treatment but thought they did not receive any benefit and the patients in 7.3 per cent, as previously mentioned, did not follow the home treatment at all, which left about four fifths of the cases in which patients reported that the treatment gave them some benefit or relief. In about two thirds of the cases patients answered without qualifi-

cations ("yes" or better) that they were benefited, and in about two fifths they were actually enthusiastic about the benefit they thought they received by carrying out the physical treatment at home.

In addition to the evaluation of the benefit in all cases, the benefit obtained in cases of rheumatoid arthritis was compared with that obtained in cases of osteoarthritis. In none of the 97 cases of rheumatoid arthritis did the patients fail to carry out the treatment or think they were harmed by it. The responses in 43.3 per cent of cases were graded plus 3; those in 27.8 per cent were graded plus 2; those in 16.5 per cent were graded plus 1, and those in 12.4 per cent were graded 0 (no benefit). The responses in 39.3 per cent of the 84 cases of osteoarthritis were graded plus 3; those in 23.8 per cent were graded plus 2; those in 8.3 per cent were graded plus 1; those in 11.9 per cent were graded 0, and in 3.6 per cent

TABLE 4.—*Effect of Number of Instructional Treatments on Results of Treatment of Rheumatoid Arthritis at Home*

No. of Instructional Treatments	No. of Cases	Treatment Still Continued or Stopped Because of Improvement	
		No. of Cases	Percentage of Cases
One	57	32	56.1
Two or more			
Outpatient routine	14	12	85.7
Hospital routine (3 weeks)	25	17	68.0
Total	39	29	74.4
Total	96*	61	63.5

* In 1 of the 97 cases of rheumatoid arthritis studied instruction was not given.

TABLE 5.—*Effect of Number of Instructional Treatments on Results of Treatment of Osteoarthritis at Home*

No. of Instructional Treatments	No. of Cases	Treatment Still Continued or Stopped Because of Improvement	
		No. of Cases	Percentage of Cases
One	69	43	62.3
Two or more	13	9	69.2
Total	82*	52	63.4

* In 2 of the 84 cases of osteoarthritis studied an instructional treatment was not given.

the patients indicated harm from the treatment. In 13.1 per cent of cases of osteoarthritis the patients did not carry out the treatment at all.

The effect of the number of instructional treatments on the results of treatment at home in cases of rheumatoid arthritis and of osteoarthritis is indicated in tables 4 and 5.

The fact that a patient carried out treatment at home for a longer period does not necessarily indicate that the treatments were more beneficial to him, since in a way, if the treatments had to be continued for a longer time, this might have meant that the patient received less benefit than another patient who improved sufficiently in a shorter time to warrant further treatment unnecessary. Furthermore, although it proved interesting to grade the patients' subjective evaluations of benefit from the home treatments, it seemed wise to find if possible a simple, more objective criterion incorporating this thought. As a result, the cases were placed in the following two groups: (1) cases in which patients were considered certainly to have

obtained some degree of benefit, since they were still carrying out the treatment a year after it was prescribed or since they stopped because of improvement, and (2) cases in which patients were considered as not proved to have obtained benefit, since they had stopped treatments for some reason other than improvement. Of course, some cases were included in the latter group in which the patients, though receiving benefit, stopped the treatments for reasons other than improvement, such as lack of equipment, facilities or aid or simple neglect. This was admittedly an arbitrary separation but seemed the simplest gross division of cases into those in which benefit certainly occurred and those in which unquestionable benefit did not occur.

Included in the group of cases of rheumatoid arthritis were those in which patients received only one instructional treatment, those in which the patients had two or more treatments and a third set of cases in which the patients, in general more seriously ill, entered the hospital and followed a definite intensive routine for three weeks, consisting of an average of twenty treatments, with instruction before dismissal on how to continue at home.

Of the cases of rheumatoid arthritis, benefit was obtained, according to our new criterion, in 56.1 per cent of the 57 cases in which patients had the usual single

TABLE 6.—*Sedimentation Rates of Erythrocytes*

Sedimentation Rate, Mm./Hr.	Rheumatoid Arthritis		Osteoarthritis	
	No. of Cases	Percentage of Cases	No. of Cases	Percentage of Cases
0- 9	14	9.3 } 21.3	23	29.1 } 68.3
10-19	18	12.0 }	31	39.2 }
20-29	18	12.0	19	24.1
30-39	19	12.7	4	5.1
40-99	66	44.0	2	2.5
100 or more	15	10.0	..	....
Total	150	100	79	100

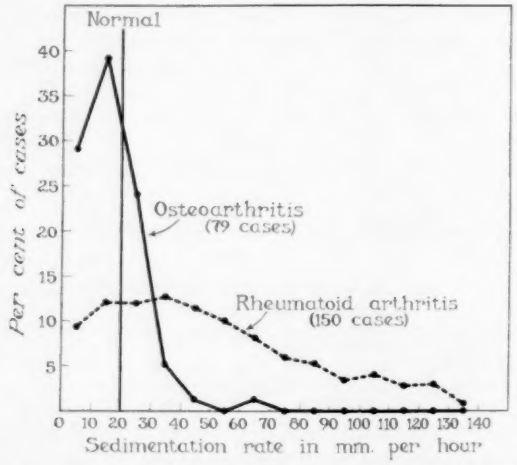
instructional treatment, in 85.7 per cent of the 14 cases in which patients had two or more instructional treatments and in 68 per cent of the 25 cases in which patients followed the hospital routine. If we total the last two sets of data, we have 39 cases of rheumatoid arthritis, in all of which two or more treatments were given and in 74.4 per cent of which benefit resulted from treatment at home. In 61 (63.5 per cent) of the total of 96 cases of rheumatoid arthritis, benefit resulted from treatment at home.

Likewise, of the cases of osteoarthritis, benefit was obtained in 62.3 per cent of the 69 cases in which patients had received just one instructional treatment and in 69.2 per cent of the 13 cases in which patients had received two or more treatments, while in the total of 52 (63.4 per cent) of the 82 cases of osteoarthritis in which patients were given instructional treatments, benefit was derived from home treatment.

The consultants in the Section on Physical Therapy have always been reluctant to give instruction without any demonstration treatment, but in 1 case of rheumatoid arthritis and in 2 cases of osteoarthritis this was done. In 2 of these 3 cases, incidentally, the patients stopped their treatment for reasons other than improvement.

A by-product of this study is observations on the sedimentation rates of the erythrocytes in 150 cases of rheumatoid arthritis and in 79 cases of osteoarthritis.

We were able to include more cases of rheumatoid arthritis here than in the main study, since we could include those cases in which questionnaires were sent and records were analyzed but in which no response was obtained. The sedimentation rates obtained in these cases are given in table 6 and in the figure. With 19 mm. per hour taken as the upper limit of normal, the sedimentation rates were more rapid than normal in about four fifths of the cases of rheumatoid arthritis but in only about a third of the cases of osteoarthritis. Whereas the sedimentation rates were more than 40 mm. per hour in only 2.5 per cent of the cases of osteoarthritis, they were more than 40 mm. per hour in more than half of the cases of rheumatoid arthritis. In the figure these same facts are set forth strikingly; the precipitous drop that occurs in the curve for the cases of osteoarthritis as soon as the rates are beyond the normal range should be compared with the slow steady drop of the curve for the cases of rheumatoid arthritis.



Sedimentation rates in cases of osteoarthritis and of rheumatoid arthritis. The line marked normal is drawn at the lower limit of the abnormally increased rates.

COMMENT

The most significant fact obtained from this study is that in 92.7 per cent of cases arthritic patients carried out physical therapy in the home as prescribed and outlined for them. Furthermore, the facts that in 64.7 per cent of cases the patients were continuing the treatments for three months or longer after dismissal from the clinic and that in 26.6 per cent of cases they were still carrying on at home a year after dismissal appeared equally interesting. These observations indicate that if physical measures are prescribed individually and in some detail, they will be followed in the home by the patient as definitely and carefully as any other form of prescribed treatment. It might be stressed that this large percentage of patients continued their regimen, in most cases, under the direction of their physician in their home locality without making any return visits to the clinic for further instruction or encouragement and without supplementary professional physical therapy.

As to the subjective response of the patients in an evaluation of benefit received, we realize that this is not proof of "cure" or even of benefit for arthritis by the

home use of physical measures. Certainly many, in fact most, of these patients were placed on a complete therapeutic regimen, and credit is not being claimed for physical therapy as the only beneficial part of the program. Nevertheless, the patient's ideas as to whether the prescribed physical measures were of benefit are valuable, because, after all, patients come to us as physicians for help. If patients as a large group state that the prescribed program of home-applied physical therapy definitely gives them benefit, then until more specific remedies can be prescribed for the different types of arthritis, we are certainly encouraged to think that it is worth while to continue prescribing home physical therapy which in 40.4 per cent of cases our patients enthusiastically say helped them and which in 79.8 per cent of cases our patients think gave them some benefit and relief.

From the more detailed analysis we can draw one other conclusion which was more or less anticipated. The patients who had rheumatoid arthritis in general were more enthusiastic about the amount of benefit they received than were those who had osteoarthritis. Yet if we compare the simpler criteria of help received by the treatment by comparing the totals in tables 4 and 5, we see that in comparable series of cases of rheumatoid arthritis and of osteoarthritis, the percentages were almost identical, 63.4 and 63.5, for cases in which patients either were still continuing the treatments after a year or had stopped because of improvement. This indicates that although the patients who had rheumatoid arthritis responded more enthusiastically, as we would expect, nevertheless, as a whole, in about the same percentage of cases the patients who had osteoarthritis and those who had rheumatoid arthritis failed to carry on because of lack of some measure of improvement or benefit.

The other really worth while conclusion from tables 4 and 5 is that it is certainly of importance, wherever possible, for patients to take more than one instructional treatment. Of the group of cases of rheumatoid arthritis, there was more improvement in those cases in which patients took two or more instructional treatments than in those cases in which patients had only one instructional treatment. At first glance there also seemed to be more improvement in the former cases than in those in which patients were given the more strenuous routine of twenty instructional treatments at the hospital. This, however, is undoubtedly due to the fact that as a group the patients for whom the hospital course was advised were much sicker. In spite of this, we see that in more cases (68 per cent as compared with 56.1 per cent) those patients who took the hospital routine of treatments did well than did their less seriously afflicted fellow patients who took only one instructional treatment. If all cases in which the patients with rheumatoid arthritis who took two or more instructional treatments are considered, we see at a glance that these patients had a significant advantage over patients who took only one instructional treatment (improvement in 74.4 per cent of cases as compared with 56.1 per cent).

In cases of osteoarthritis a similar difference in percentage occurs, though not as great; there was improvement in 69.2 per cent of the cases in which patients took more than one instructional treatment as compared to 62.3 per cent of the cases in which patients had only the one. This only means that in osteoarthritis it is not as important, though still of some possible value, to encourage the patient to take an extra instructional treatment or two.

The physical measures advised for home use are all simple and may be adapted to the most meager facilities; yet they must be learned accurately and carried out precisely if they are to give maximal benefit. The extra instructional treatment or two seems to impress on the patient to a greater extent just what and how he is to carry on at home. Many patients think they can just read instructions and follow

them. Our experience indicates that when, in addition to printed instructions, a demonstration treatment, or better two, is given the patient learns more readily just how he should carry out the prescribed measures. He is then more likely to continue with the treatments and to derive the desired benefit. When a patient does take a couple of treatments weekly from a skilled technician, as is advised whenever possible, it is important that he be warned that any such program is entirely inadequate if the home part of the routine between professional treatments is neglected.

Table 6 is included merely as an interesting summary of the sedimentation rate of the erythrocytes in comparable series of cases of rheumatoid arthritis and of osteoarthritis. In general, the distribution of the sedimentation rates as we found them in rheumatoid arthritis and in osteoarthritis was about the same as those already reported in the literature.[2] The rheumatoid arthritis was of all stages, and this accounts for the fact that sedimentation rates were within the normal range in 21.3 per cent of the cases. In 68.3 per cent of the cases of osteoarthritis the sedimentation rate was within the normal range, and in only 2 cases was the sedimentation rate more than 40 mm. per hour. The sedimentation rate is not a specific test and is elevated under many circumstances, and, as would be expected, we found that associated and coincidental processes accounted for many of the sedimentation rates that were more than normal in the cases of osteoarthritis.

SUMMARY

A follow-up study was made in 218 cases of all types of arthritis in which home physical therapy was prescribed. Of these 218 cases, patients in 92.7 per cent carried out the prescribed treatments at home and in 64.7 per cent continued the treatments for three months or longer. Patients who received more than one instructional treatment were more likely to carry on the regimen at home with improvement than were those who had only one.

In approximately 4 out of 5 cases of arthritis patients thought they were benefited by the use of home physical measures, and in 2 out of 5 they were definitely enthusiastic in their replies. In general, patients who had rheumatoid arthritis were more enthusiastic about the benefit received than were those who had osteoarthritis, but on rough analysis the beneficial results obtained by both groups were comparable.

Data on the sedimentation rates in 150 cases of rheumatoid arthritis and in 79 cases of osteoarthritis were presented.

CONCLUSIONS

To be effective in the therapeutic program of a case of arthritis, physical therapy should be carried on daily over long periods of time in the home. Each patient should be prescribed for individually by a physician and should be instructed in one or more demonstration treatments just how he is to carry on at home. When physical therapy is prescribed with proper care for arthritic patients and the patients are instructed with sufficient detail, a gratifying number of them continue the treatments at home and feel that they are benefited in so doing.

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EFFECT OF EXERCISE ON BLOOD PYRUVIC ACID

OBSERVATIONS ON TRAINED AND UNTRAINED NORMAL SUBJECTS AND ON PATIENTS WITH HEART DISEASE AND WITH HYPERTENSION

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An increase of lactic acid in the blood and tissues following exercise is one of the classic observations in physiology. Since this discovery an extensive literature has accumulated on changes in lactic acid as related to work, training and fatigue. More recently Dill and his group[1] have suggested that it be employed as an index of cardiovascular fitness. However, it is now the considered opinion of most biochemists[2] that pyruvic acid, and not lactic acid, is the core of the carbohydrate metabolism of tissues. In the breakdown of dextrose by the tissues all reactions appear to revolve around pyruvic acid as the pivotal point. Further interest has been attached to pyruvic acid because of Peters'[3] discovery that the presence of vitamin B_1 is necessary for its oxidation. This displacement of lactic acid in the scheme of the carbohydrate metabolism of tissues by pyruvic acid led to the formulation of this work.

METHOD AND MATERIAL

A standard exercise of fifty ascents and descents in one hundred seconds over a two step contrivance,[4] with the blood level of pyruvate determined while the subject was resting and ten and sixty minutes after the exercises, was performed by 11 wrestlers and track men aged 18 to 21 from the University of Chicago, 10 persons aged 19 to 54 engaged in sedentary occupations, 10 patients aged 21 to 48 of functional classes II and III with cardiac disease and enlargement and 9 hypertensive patients aged 31 to 51 of functional class I without cardiac enlargement or detectable renal involvement but with systolic blood pressures exceeding 200 mm. of mercury.

Blood pyruvate was analyzed by Friedemann's modification[5] of Lu's method.[6] Preliminary investigation revealed the ten and the sixty minute period to be optimum for study.[7]

From the Department of Medicine of the University of Chicago.

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7. These time intervals were selected at the suggestion of Dr. Theodore E. Friedemann, of the Abbott Foundation for Medical Research, Northwestern University (personal communication).

RESULTS

Ten Minute Changes in Blood Pyruvate (tables 1 through 4).—In the trained group the mean ten minute change in blood pyruvate was — 3.6 per cent, and the blood pyruvate of only 3 subjects of 11 showed a rise after ten minutes. These increases were small and insignificant, as compared with the ten minute increases for the other groups.

All the subjects in the untrained group showed marked rises in blood pyruvate after ten minutes, as evidenced by a mean rise of + 53.3 per cent and a range of + 28 to + 101 per cent.

TABLE 1.—*Absolute and Percentage Changes in Pyruvate in the Blood of Trained Subjects Ten and Sixty Minutes After Moderate Exercise*

Subject No.	Age, Yr.	Blood Pyruvate, Mg./100 Cc. During Rest	10 Minutes After Exercise	60 Minutes After Exercise	Δ % 10 Minutes	Δ % 60 Minutes
1	18	0.50	0.56	0.50	+12	0
2	20	0.63	0.56	0.51	−11	−19
3	20	0.71	0.78	0.71	+10	0
4	21	0.75	0.75	0.63	0	−16
5	20	0.91	0.90	0.90	− 1	− 1
6	20	1.00	0.90	0.71	−10	−29
7	20	1.15	1.05	0.85	− 9	−26
8	19	1.23	1.16	0.78	− 6	−37
9	19	1.51	1.20	1.45	−21	− 4
10	20	1.78	1.70	1.58	− 5	−11
11	20	0.86	0.90	0.66	+ 5	−23

TABLE 2.—*Absolute and Percentage Changes in Pyruvate in the Blood of Untrained Subjects Ten and Sixty Minutes After Moderate Exercise*

Subject No.	Age, Yr.	Blood Pyruvate, Mg./100 Cc. During Rest	10 Minutes After Exercise	60 Minutes After Exercise	Δ % 10 Minutes	Δ % 60 Minutes
12	45	0.60	1.00	0.63	+67	+ 5
13	35	0.60	0.86	0.53	+43	−12
14	19	0.71	1.43	0.80	+101	+13
15	28	0.75	1.06	0.80	+41	+ 7
16	54	0.80	1.30	0.90	+63	+13
17	24	0.86	1.10	0.56	+28	−35
18	24	0.90	1.36	0.86	+51	− 4
19	28	0.90	1.38	1.00	+53	+11
20	20	0.91	1.21	0.60	+33	−34
21	30	0.90	1.58	0.71	+53	−21

In the group of subjects with heart disease the ten minute values for blood pyruvate were also all substantially elevated, with a mean of + 46 per cent and a range of + 23 to + 86 per cent.

Again, in the hypertensive group there were definite increases at ten minutes. This group had the highest ten minute mean, + 63.6 per cent, and the highest single ten minute value, + 131 per cent. The range of the ten minute values was + 26 to + 131 per cent.

Sixty Minute Changes in Blood Pyruvate (tables 1 through 4).—At the end of an hour all subjects in the trained group had decreases ranging from — 1 to — 37 per cent, with the exception of 2 who had no change from the initial level. The mean sixty minute change was — 15.1 per cent. Four of the trained subjects had significantly higher pyruvate levels while they were resting than that previously reported as normal. The significance of this is not clear, other than

that it may in some way accompany the chemical changes of training, but it makes conclusions regarding the changes for these 4 subjects difficult to draw.

In the untrained group the range of the sixty minute differences was + 13 to — 35 per cent, with a mean of — 5.7 per cent.

The patients with heart disease had a sixty minute mean of + 16.8 per cent, and this is probably a real difference, as only 2 of 10 patients showed negative one hour values (and these were small) and 3 had values higher than + 40 per cent.

The mean of the sixty minute values of the hypertensive subjects was + 0.3 per cent, or for all practical purposes 0.

TABLE 3.—*Absolute and Percentage Changes in Pyruvate in the Blood of Patients with Heart Disease (Functional Classes II and III) Ten and Sixty Minutes After Moderate Exercise* *

Subject No.	Age, Yr.	Type of Heart Disease	Functional Class	Blood Pyruvate, Mg./100 Cc. During Rest	10 Minutes After Exercise	60 Minutes After Exercise	Δ % 10 Minutes	Δ % 60 Minutes
22	28	RV	II	0.63	0.86	0.63	+37	0
23	21	RV	II	0.80	1.30	0.90	+63	+13
24	37	RV	II-III	0.86	1.06	0.98	+23	+14
25	34	RV	III	0.90	1.31	1.33	+46	+48
26	24	RV	III	0.98	1.76	1.46	+80	+49
27	48	RV	III	1.00	1.86	1.43	+86	+43
28	29	RV	II	1.00	1.23	1.03	+23	+ 3
29	23	RV	III	1.10	1.46	1.06	+33	— 4
30	47	HA	II	0.71	0.90	0.70	+27	— 1
31	35	H	II-III	1.20	1.70	1.23	+42	+ 3

* The following abbreviations have been employed: RV, rheumatic valvular heart disease; H, hypertension, and HA, hypertension with angina.

TABLE 4.—*Absolute and Percentage Changes in Pyruvate in the Blood of Patients with Hypertensive Vascular Disease (Functional Class I) Ten and Sixty Minutes After Moderate Exercise*

Subject No.	Age, Yr.	Functional Class	Blood Pyruvate, Mg./100 Cc. During Rest	10 Minutes After Exercise	60 Minutes After Exercise	Δ % 10 Minutes	Δ % 60 Minutes
32	51	I	1.13	1.46	0.86	+29	—24
33	51	I	0.75	1.73	0.90	+131	+20
34	40	I	1.03	1.46	0.90	+42	—13
35	39	I	1.13	1.95	0.95	+76	—16
36	47	I	1.10	2.10	1.10	+91	0
37	39	I	0.63	1.63	0.83	+64	+32
38	42	I	0.56	1.00	0.63	+79	+13
39	31	I	0.75	1.01	0.76	+35	+ 1
40	41	I	0.78	0.98	0.70	+26	—10

COMMENT

Statistical and Correlative Analysis.—All the data were subjected to statistical analysis.[8] The trained subjects were of approximately the same age and of equal degree of training. As a group their ten and sixty minute changes in blood pyruvate were not statistically significant. But on an individual basis the varied responses of pyruvate of this group, as well as those of the untrained subjects, may be indicative of various degrees of cardiovascular fitness. Correlation of results of individual physical endurance tests with the changes in blood pyruvate could possibly have been revealing in this respect, but it was not attempted in this study. The track men and the wrestlers showed no difference as a group in either their ten or their sixty minute response of blood pyruvate to the exercise.

8. Dr. Frederic T. Jung, of the Department of Physiology, Northwestern University, aided me in the statistical calculations.

The ten minute changes in blood pyruvate of the untrained subjects and of the patients with heart disease and with hypertension were found to be statistically significant. None of the groups, with the exception of the patients with heart disease, could be shown to have statistically significant sixty minute changes. Fisher's rule [9] stipulates that a critical ratio of 2 represents statistical significance. The calculated critical ratio of the sixty minute changes of the patients with heart disease was 1.42, and this is close enough to 2 to place the sixty minute changes of the patients with cardiac disease in the realm of "practical" significance.

In the untrained group the subjects were all closely alike in daily physical activity, but there was a purposeful wide age variation to match the age range of the patients with heart disease and with hypertension. That the ten minute changes were significant would indicate that age was not a modifying factor in these changes. The ten and sixty minute changes of the other groups were similarly not influenced by age.

In the patients with heart disease and with hypertension there were individual differences based on such variables as duration, type and magnitude of symptoms; functional capacity; cardiac enlargement; degree of cardiac damage and stress; number of failures, and lability of blood pressure. It is usually impossible to select a group of patients who are standardized on all the variables of clinical experimentation. In the main these variables were related to the changes in blood pyruvate. The patients of functional class III with heart disease (table 3) had the highest sixty minute levels, and the duration of the cardiac symptoms and the number of cardiac failures of each patient tended to be expressed by the greater ten and sixty minute changes. This is an encouragement to further investigation, as there is need for precise measurement of the functional capacity of a patient with cardiovascular disease in terms of the actual chemical processes that the body utilizes to perform work.

Pulse recovery time following exercise did not seem to correlate with the changes in blood pyruvate except for the hypertensive patients whose ten minute changes and pulse recovery times were of the same magnitude. The group of patients with heart disease was the only one that showed a similar trend in the ten and the sixty minute changes in blood pyruvate for each subject; a high ten minute increase in this group seemed to correspond to a high sixty minute increase.

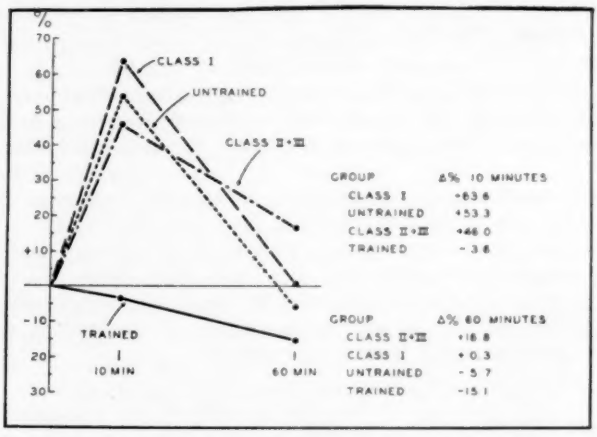
All the hypertensive patients led sedentary lives except 1 truck driver and 1 maintenance man. The former daily lifted heavy objects, while the latter walked about 16 miles (26 kilometers) daily in his work. It is of interest that even though these men were in some form of training, their changes in blood pyruvate were in no way similar to those of the more rigidly trained subjects. The truck driver who daily did some heavy work had a ten minute rise of + 64 per cent and a sixty minute change of + 32 per cent, the latter value being the highest in the group. No explanation for this is available.

Comparisons of Group Means (figure).—The ten minute values of the trained group contrasted with those of the other groups, and the initial "high normal" levels of some of the trained subjects indicate a change in the mechanism of carbohydrate utilization of trained persons as opposed to that of subjects in the other groups, whose hearts *only* are working overtime. This observation suggests a clue to the complex chemical changes involved in "training" and "compensation." These ten minute changes could also conceivably be used as a practical criterion of physical fitness.

9. Dunn, H. L.: Application of Statistical Methods in Physiology, Physiol. Rev. **9**:275 (April) 1929.

By doing some calculations made possible by what is known about the work of the heart, it can be shown that the heart of a hypertensive person probably does more work in twenty-four hours than does the heart of a trained man doing his usual exercise. From this we might expect the hypertensive person to be in some form of training. But the changes in blood pyruvate of the two are notably different. It would appear that the use of body muscles is necessary to achieve the state of training. Thus the old thought that patients with heart disease should exercise up to their respective limits may not have been too far fetched.

The mean sixty minute change in blood pyruvate of the trained subjects was — 15.1 per cent of the resting levels, that of the untrained subjects — 5.7 per cent, that of the hypertensive subjects 0 and that of the subjects with cardiac disease + 16.8 per cent. The order of progression from negative to positive sixty minute changes is more or less in keeping with the cardiac function of each group. These sixty minute changes also suggest a possible index of cardiovascular fitness, and further, this test could presumably be used to follow the course of a patient



Mean changes in blood pyruvate after moderate exercise.

with heart disease. This is further supported by the previously mentioned fact that patients of functional class III with heart disease with the poorest cardiac function (with 1 exception) had the highest positive sixty minute changes. This also fits in with a recent paper in which I [10] reported high blood levels of pyruvate occurring in patients with heart failure.

Comparisons of Lactate.—The literature of changes in blood level of lactic acid following exercise indicates that lactate both in trained and in untrained subjects increases only after strenuous exercise and not after moderate exercise.[11] In this study blood pyruvate increased after only light to moderate exercise as much as 131 per cent. Thus, blood pyruvate is available for study as a chemical indicator of physiologic changes related to exercise in untrained subjects on whom severe exercise would be a hardship and in patients who are not capable of undertaking the severe exercise that determination of blood lactate requires.

10. Yanof, Z. A.: Blood Pyruvic Acid in Heart Disease, Arch. Int. Med. **69**:1005 (June) 1942.

11. Dill, D. B.: The Economy of Muscular Exercise, Physiol. Rev. **16**:263 (April) 1936.

In the trained subjects the mean ten and sixty minute percentage changes were apparently not significant and thus are comparable to the stability of blood lactate after moderate exercise. However, there are no reported changes in lactate that are comparable to the individual negative sixty minute changes in blood pyruvate of the trained group. Blood levels of lactate during rest apparently do not increase with training and so are not comparable to the 4 elevated levels of pyruvate during rest encountered in this study.

The increase of pyruvate in the blood after both moderate and severe [12] exercise, and the failure of lactate to increase in the blood except after exhausting exercise indicate that pyruvate is an important and obligatory intermediate (if not the principal) metabolite in the chemical mechanism of any muscular contraction, with lactate coming into play as a secondary auxiliary system when the anoxic conditions of heavy exercise are present. This fits in with the present day concept of the central place that pyruvic acid occupies in the carbohydrate metabolism of tissue, and is further inferential support of the foregoing observations on the greater sensitivity of pyruvate level in exercise physiology.

Analysis of blood pyruvate is also more accurately and more easily accomplished than analysis of lactate.

CONCLUSIONS

Ten minutes after moderate exercise a group of trained subjects had no significant change in blood level of pyruvate, while untrained subjects and patients with heart disease and with hypertension had in contrast marked rises of pyruvate in the blood.

The sixty minute changes of the group of patients with heart disease were significantly high and were proportional to functional capacity.

Blood pyruvate measurably increases after moderate exercise in untrained subjects and in patients with cardiovascular disease, while lactate does not, and so estimations of pyruvate can be utilized in the study of cardiovascular fitness of untrained subjects and patients who are not capable of undertaking the strenuous exercise that measurement of blood lactate requires.

Dr. Emmet B. Bay offered guidance and criticism.

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12. P. E. Johnson and H. T. Edwards (Lactate and Pyruvate in Blood and Urine After Exercise, J. Biol. Chem. **118**:427 [April] 1937) and T. E. Friedemann and C. J. Barborka (The Significance of the Ratio of Lactic to Pyruvic Acid in the Blood After Exercise, ibid. **141**:993 [Dec.] 1941) have reported increases in blood pyruvate as accompanying increases in blood lactate in trained subjects after severe exercise.

LIMITATIONS OF THE ERYTHROCYTE SEDIMENTATION TEST IN TUBERCULOSIS

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Since the introduction of the erythrocyte sedimentation test into clinical practice numerous publications have dealt with its value in the diagnosis, prognosis and treatment of tuberculosis. The overwhelming majority of articles reflect the following convictions: 1. It is a reliable gage for the detection of active pulmonary tuberculosis. 2. The sedimentation rate of erythrocytes is directly proportionate to the extent of tuberculosis. 3. The test conforms rather snugly to the underlying pathologic process, being more rapid in association with the predominantly exudative type of lesion than in the case of productive or fibrosing tuberculosis. 4. An increased rate of erythrocyte sedimentation is of direct prognostic value and a sensitive signal of an oncoming spread of the disease. 5. In cases of pulmonary tuberculosis in which collapse therapy is instituted the test is a competent index of improvement which may not be detectable by other clinical means.

For the purpose of ascertaining the clinical value of this test we have analyzed the records of 2,640 tuberculous patients who were under observation at this sanatorium during the past four and a half years. We were prompted to make this study by finding definite discrepancies between the results of the sedimentation test and other laboratory and clinical data used as indicators of the activity of the disease. Roentgenologically demonstrable active tuberculous lesions and gastric contents or sputum positive for tubercle bacilli together with a normal sedimentation rate were encountered in infants, children, adolescents and adults. In some patients whose disease was discovered through health surveys normal sedimentation velocity was encountered in the presence of active pulmonary tuberculosis with sputum positive for tubercle bacilli. We have found also that as an indicator for the onset of the reinfection type of tuberculosis in nurses exposed to tuberculous patients a normal erythrocyte sedimentation rate is of questionable value and that it does not compare favorably with serial roentgenograms of the chest. Therefore, in view of the unhesitating reliance on this procedure by many physicians who are seeing tuberculous patients, we thought it justifiable to call attention to our observations.

Extensive clinical and experimental studies have brought out various theories concerning changes in the sedimentation rate. Fahraeus [1] expressed the opinion that they are due to qualitative changes in the serum globulins, particularly in fibrinogen. Ernstene [2] demonstrated that variations in the amount of fibrinogen and not in its quality are the decisive factors. Hille [3] expressed the belief that

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1. Fahraeus, R.: Suspension Stability of Blood, Acta med. Scandinav. **55**:3, 1921.

2. Ernstene, C.: Erythrocyte Sedimentation, Plasma Fibrinogen and Leukocytosis as Indices of Rheumatic Infection, Am. J. M. Sc. **153**:12, 1930.

3. Hille, G.: Colloid Stability and Sedimentation Test in Infants, Monatschr. f. Kinderh. **28**:137, 1924.

besides the colloid balance of the blood the number of red cells and the amount of hemoglobin are of significance in this respect. Early investigators suggested that the sedimentation rate is influenced by the difference in the electrical potential between the negatively charged red cells and the positively charged proteins of the plasma; greater negative charge of the red cells was encountered in serum albumin than in serum globulin or in serum fibrinogen. Bernou [4] regarded the viscosity of the whole blood and not that of the plasma alone as the chief determining factor. Accordingly, an increase in the volume of the individual blood corpuscles, which increases the viscosity, causes a retardation of the settling, while an increase in the globulin, which forms large molecules at the expense of the albumin, reduces viscosity and leads to a rapid sedimentation of the red cells. Cutler and his associates [5] made a critical appraisal of the role anemia plays in the sedimentation of erythrocytes. They came to the conclusion that anemia has little to do with it and that increased sedimentation is caused by the erythrocytes forming large aggregates, or rouleaux. They stated that the formation of aggregates of erythrocytes is the function of the plasma and is specific for any given plasma; the latter is little influenced by the size, shape or number of erythrocytes in suspension.

In the evaluation of this test one also has to keep in mind that a number of incidental factors influence its outcome. The settling of the red cells is faster in women than in men [6]; also, Bertrand and Rousseaux [7] reported that there are rhythmic variations in the sedimentation rate during the phases of the menstrual cycle. There is a premenstrual and menstrual increase induced by an increase in the amount of fibrinogen. The rate is increased during pregnancy [8] and in old age.[9] The possible effect of the endocrine glands was also investigated. Runnström and Schow [10] found that accelerated settling occurred in experimental animals after thyroidectomy. It was demonstrated by Lockett [11] that exercise is followed by an accelerated settling; this effect may persist for some time. He also observed that the rate is decreased during digestion, reaching its slowest progress in one to one and a half hours after intake of food. A correlation between the carbon dioxide content of the venous blood and the sedimentation rate was noted by Freeman.[12] Pinner and his associates [13] emphasized the fact that rather wide variations occur from day to day in normal persons. Hoverson and Peterson [14] offered an explana-

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8. Bland, P. B.; Goldstein, L., and First, A.: Sedimentation Test in Pregnancy and Puerperium: Study of Five Hundred and Forty Patients, Surg., Gynec. & Obst. **50**:429, 1930.

9. Lasch, F.: Study of the Cause of Acceleration of the Sedimentation Rate in the Aged, Wien. Arch. f. inn. Med. **22**:155, 1931.

10. Runnström, J., and Schow, S. A., cited by van Antwerp, L. D.: Repeated Sedimentation Tests, Am. J. Dis. Child. **48**:814 (Oct.) 1934.

11. Lockett, M. F.: Study of Certain Factors Affecting the Sedimentation Rate, Brit. J. Tuberc. **31**:31, 1937.

12. Freeman, H.: Sedimentation Rate of Blood in Schizophrenia, Arch. Neurol. & Psychiat. **30**:1298 (Dec.) 1933.

13. Pinner, M.; Knowlton, K., and Kelly, R. G.: Sedimentation Rate of Erythrocytes: Its Relation to Fibrin Value and Cholesterol Content and Its Application in Tuberculosis, Arch. Path. **5**:810 (May) 1928.

14. Hoverson, E. T., and Peterson, W. F.: Meteorologic Effects on the Sedimentation Rate of the Erythrocytes, Am. J. M. Sc. **188**:455, 1934.

tion for this observation. They postulated that meteorologic conditions induce demonstrable changes in the human body which may be measured by chemical examination of the blood and that these chemical alterations in the blood account for the daily variations in the erythrocyte sedimentation rate.

Experimental work on tuberculous animals revealed that both immunity and the allergic status may have some bearing on the outcome of the test. Dwelshawers [15] found that the sedimentation rate remained normal in rabbits which were first inoculated with an avirulent strain of tubercle bacilli and inoculated subsequently with virulent bovine tubercle bacilli, while in nonimmunized controls the sedimentation rate was rapid. On the other hand, Freund and Frank [16] demonstrated that the injection of old tuberculin into tuberculous rabbits was followed by a considerably increased sedimentation rate.

There is no doubt that the erythrocyte sedimentation rate is subject to the same physical laws that apply to particles suspended in fluid medium, as expressed by Stokes's formula $V = \frac{2}{9} g \frac{S - S_1}{u} r^2$, in which V = the velocity of fall, g = the gravitation constant, S = the specific gravity of the red blood cells, S_1 = the specific gravity of the blood plasma, u = the absolute viscosity of the plasma and r = the radius of the rouleaux, or aggregates of erythrocytes. According to this formula, the sedimentation rate is directly proportional to the square of the radius of the red cell aggregates and inversely proportional to the viscosity of the plasma.

It must be kept in mind that certain factors which influence the chemical activity of the body in some particular manner—in health or during the course of tuberculosis—may play a part in the outcome of the sedimentation test. Therefore, no correct interpretation of the result is possible unless due consideration is given to the potential effect of these factors. If this is so, it is evident that variations in the erythrocyte sedimentation rate in a tuberculous person are bound to reflect the influences of factors that may have nothing to do with the type, extent and course of the tuberculous process.

The limitations of the erythrocyte sedimentation test in tuberculosis are best illustrated by brief summaries of representative cases.

REPORT OF SIX CASES

CASE 1.—*Active primary tuberculosis in a white infant with a normal erythrocyte sedimentation rate.*

A. M., an infant white girl aged 8 months, was admitted to the sanatorium with the diagnosis of an active primary tuberculous infection, with an involvement of the hilar lymph nodes and the perihilar pulmonary parenchyma. The cutaneous reaction to tuberculin was strongly positive. Aspirated gastric contents were positive for tubercle bacilli on culture, and at the same time the erythrocyte sedimentation rate was normal. Because of the positive culture she was treated at the sanatorium for fifteen months; recovery was complete.

CASE 2.—*Active pulmonary tuberculosis in an adolescent white girl with a normal erythrocyte sedimentation rate.*

V. J., a white girl aged 14, was admitted to the sanatorium with complaints of cough, thoracic pain, loss of strength and night sweats. A roentgenogram of the chest showed a parenchymal infiltration in the apical and the subapical area of the left lung. Her temperature was subfebrile occasionally during the first two months of her stay. Aspirated gastric contents were positive for tubercle bacilli on culture and on inoculation into guinea pigs and her erythrocyte sedimentation rate was normal on admission.

15. Dwelshawers, F.: Blood Sedimentation and Antibody Response in Rabbits, Compt. rend. Soc. de biol. **123**:549, 1936.

16. Freund, J., and Frank, D. E.: Sedimentation Rate of Red Blood Cells in Tuberculous Rabbits Injected with Tuberculin, J. Immunol. **24**:247, 1933.

CASE 3.—*Toxic symptoms in pulmonary tuberculosis in a white woman with a normal erythrocyte sedimentation rate.*

G. S., a white woman aged 39, was admitted with moderately advanced active pulmonary tuberculosis. She complained of chills, fever, night sweats, anorexia, loss of weight, weakness and fatigue. Physical examination and a roentgenogram showed active disease in the upper one third of both lungs. The sputum was positive for tubercle bacilli on culture, and the erythrocyte sedimentation rate was normal.

CASE 4.—*Caseous pulmonary tuberculosis in a Negro with a normal erythrocyte sedimentation rate.*

B. P., a Negro aged 48, began to cough and raise greenish yellow mucoid sputum nine months before admission; he expectorated about 1 fluidounce (30 cc.) of sputum a day. He complained of moderate cough and loss of strength and weight. A roentgenogram showed a caseous infiltration in the right lung, extending to the third rib anteriorly and to the sixth dorsal spine posteriorly. On admission his sputum was negative for tubercle bacilli, but aspirated gastric contents were positive for tubercle bacilli on culture and on inoculation into guinea pigs. At the same time his erythrocyte sedimentation rate was normal.

CASE 5.—*Pulmonary tuberculosis with honeycomb cavitation in a white woman with a normal erythrocyte sedimentation rate.*

E. D., a white woman aged 33, was admitted to the sanatorium with the complaints of persistent cough and loss of weight of four months' duration, also blood streaking of sputum and dyspnea. The results of physical examination indicated an active tuberculous process in the upper third of the left lung. A roentgenogram showed a heavy fibrocaseous infiltration in the middle third and the subapical region of the left lung with honeycombing. The sputum was classed as II on the Gaffky scale examination; the erythrocyte sedimentation rate was normal.

CASE 6.—*Far advanced pulmonary tuberculosis with a large open cavity in a white man with a normal erythrocyte sedimentation rate.*

J. S., a white man aged 55, was admitted with the complaints of moderate cough, expectoration and dyspnea. Numerous moist rales were heard over the upper third of the right lung anteriorly and throughout posteriorly, also over the apical area of the left lung. A roentgenogram revealed a bilateral fibrocaseous infiltration largely confined to the upper half of each lung; there was a cavity measuring 45 by 70 mm. in the upper lobe of the right lung. His sputum was positive for tubercle bacilli on direct examination, and the erythrocyte sedimentation rate was normal.

COMMENT

A normal sedimentation rate may occur in the presence of considerable destruction of tissue, honeycomb cavitation, a large solitary excavation or multiple cavities. We have noted during the course of various measures of collapse therapy that in some of our patients the originally accelerated sedimentation rate returned to normal shortly after the institution of treatment, although simultaneously clinical data showed that pulmonary cavities remained open and the disease continued to be active.

Furthermore, we have encountered normal sedimentation velocity in a patient with bacteriologically proved tuberculous empyema and in patients with pulmonary tuberculosis and the following tuberculous complications: cervical adenitis, arthritis, bronchiectasis, renal tuberculosis, tuberculous pleurisy with effusion, tuberculoma of the larynx and lupus vulgaris. Normal rates were recorded for a patient with active pulmonary tuberculosis superimposed on silicosis and a patient with diabetes mellitus complicated by pulmonary tuberculosis. Also, we have encountered normal sedimentation of erythrocytes in a patient with draining tuberculous cervical adenitis, tuberculous tenosynovitis, pleurisy with effusion and tuberculosis of the bone and in a patient with bilateral renal tuberculosis.

Of the 2,640 tuberculous patients included in this study, a normal sedimentation rate and active disease were found simultaneously in 212, or 8 per cent. Of these patients, 206 had pulmonary tuberculosis and 6 had extrapulmonary tuberculosis.

Of the patients with pulmonary tuberculosis 13 were not classified as to the stage of their illness because of the concurrent measures of collapse therapy applied to the lungs. The remaining 193 come under the following classification of the National Tuberculosis Association: minimal infection 18, or 9.3 per cent; moderately advanced infection 95, or 49.2 per cent; far advanced infection 51, or 26.4 per cent, and active primary infection 29, or 15 per cent.

From the review of the illustrative cases and other data presented in this paper one is justified in concluding that the result of the erythrocyte sedimentation test does not reflect the true pathologic status of tuberculosis. Consequently, this test cannot be considered an accurate or reliable index for the management of a tuberculous patient, that is, for prescribing necessary rest in bed or permissible exercise, for planning collapse therapy or for making the periodic follow-up examinations of patients with "apparently arrested" tuberculosis.

SUMMARY

A study of the erythrocyte sedimentation rate of 2,640 tuberculous patients observed during the past four and a half years revealed that 8 per cent of them had a normal sinking velocity.

Simultaneous occurrence of active tuberculosis and a normal sedimentation rate was observed in all age groups and in patients with primary infection as well as in ones with a reinfection type of disease.

The erythrocyte sedimentation rate does not parallel the type and the extent of tuberculosis. Normal rates were encountered in association with minimal, moderately advanced and far advanced infection, with productive and with exudative pulmonary tuberculosis and with solitary or multiple cavities. The size of the pulmonary cavities varied from honeycombing to cavities 45 mm. by 70 mm. in diameter.

Sputum positive for tubercle bacilli examined directly or after homogenization or aspirated gastric contents positive for these organisms (on culture or on inoculation into guinea pigs) were encountered in association with a normal sedimentation rate.

The type and length of a regimen based on rest in bed cannot be gaged by the sedimentation test, because the rate may return to normal shortly after the beginning of treatment or much earlier than the healing of the parenchymal process takes place.

The eligibility of a patient to become ambulatory and undergo pneumothorax treatment should not be decided on the basis of a normal sedimentation rate unless the results of other procedures are corroborative, including aspiration of gastric contents that are repeatedly negative for tubercle bacilli on culture or on inoculation into guinea pigs.

During the course of various measures of collapse therapy the sedimentation rate may return to normal while cavities remain open and the tuberculous process is still active.

CONCLUSIONS

1. It is our impression that the clinical value of the erythrocyte sedimentation test in tuberculosis is greatly overestimated.

2. Our observations indicate that it has considerable limitation; therefore, it should not be used as an independent index in the management of tuberculous patients.

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ESTROGEN, DIABETES AND THE MENOPAUSE

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In the several years since the work of Evans and co-workers [1] and of Houssay and co-workers [2] the relationship of the anterior lobe of the pituitary gland to carbohydrate metabolism has been rather firmly established. More recently Young [3] has been able to produce permanent diabetes by the use of potent extracts of the anterior lobe of the pituitary gland prepared at freezing temperatures. The pancreas of animals with such diabetes was found to show an atrophy of the islands of Langerhans and by actual assay very little or no insulin.

The menopause is associated with hyperactivity of the anterior lobe of the pituitary gland. Thus any of its chemical products or biologic functions may be increased. If among these products the "diabetogenic" factor is increased it can produce diabetes or aggravate an existing diabetes either by its antagonistic action to insulin or, more fundamentally, by its effect functionally or even anatomically in producing hydropic and hyaline degeneration or atrophy of the islands of Langerhans.

During the menopause the subjective and objective vasomotor disturbances and the increased amount of gonadotropic hormone in the blood and urine are evidences of the overactivity of the anterior lobe of the hypophysis. Such overactivity seems to be in inverse proportion to the atrophy and diminished function of the ovaries and the consequent decrease of available estrogenic follicular hormone. The overfunctioning anterior lobe of the pituitary gland then secretes an overabundance of all its hormones in addition to the gonadotropic, and one of these is the "diabetogenic" hormone.

Tuttle [4] observed that the onset of diabetes coincided with that of the menopause in 38 of 72 diabetic women. Joslin [5] attributed the preponderance of diabetes in middle-aged women to the obesity so frequently occurring at the menopause.

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The cases reported were presented at meetings of the Society of Alumni of Lebanon Hospital and the North Bronx Medical Society.

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4. Tuttle, E.: Diabetes Mellitus, New York State J. Med. **37**:636-642 (April 1) 1937.

5. Joslin, E. P.: An Appraisal of the Present Treatment of Diabetes, J. A. M. A. **97**:595-602 (Aug. 29) 1931.

In general, diabetes has an onset at this age period even in the male, and this, together with the obesity at this time, may point to the pituitary factor as of importance in at least a proportion of cases of diabetes.

Estrogen exerts an inhibitory effect on the anterior lobe of the pituitary gland. The administration of this substance, therefore, reduces pituitary hyperactivity during the menopause. This inhibitory effect has been demonstrated repeatedly and can be utilized as a means of assaying the proper dosage of estrogen. The dose is that which will result in disappearance of the gonadotropic factor from the urine. However, inhibition is not limited to the gonadotropic factor. Zondek [6] demonstrated inhibition of growth in infantile rats by administration of estrogen. He stated the belief that the effect of estrogen on the pituitary gland manifests itself first by reduction of its gonadotropic function and then by a reduction of its other functions.

Barnes, Regan and Nelson [7] have shown that the administration of amniotin to female dogs previously made diabetic by pancreatectomy renders them either nondiabetic or only mildly diabetic. Mazer and Israel [8] were among the first to report the ameliorating effect of estrogen on the diabetes, having noted this in 3 of their 51 menopausal patients treated with 2,000 rat units of estrogen as estradiol benzoate every four days. This amount of estrogen controlled the associated diabetes of these 3 women without the use of insulin, and any decrease in the dose of estrogen resulted in a return of hyperglycemia and glycosuria. Spiegelman [9] controlled the diabetes of 9 women by the administration of 10,000 international units of estrogen twice weekly. Goldman, Goldman and Kurzrock [10] noted the disappearance of the glycosuria and hyperglycemia of a diabetic patient who was 1 of 8 women treated with estrogen for the relief of menopausal symptoms and concomitant hyperthyroidism. Collens and co-workers [11] made an adverse report in a trial of amniotin on 7 persons with diabetes, 1 a male and all unselected as to menopause and age. They used a very small dose (100 to 400 rat units of estrogen). Gessler, Halsted and Stetson [12] selected for treatment 5 diabetic patients all past the menopause. In the first 2 diabetes began at the time of the menopause. In these patients there was an effect on the blood sugar. However, the complete results of the therapy were indefinite. These workers concluded that the conflicting results reported in the literature might be due to an inability to choose the proper type of diabetes for such treatment. Cantilo [13] obtained a 100 per cent good

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response in 40 diabetic women in the menopause using estrogen and progesterone three times a week. He emphasizes the necessity of separating this "special type of climacteric diabetes." Our work was undertaken with this point in view.

In the diabetic clinic at Lebanon Hospital about 90 per cent of the patients are women who either have passed the menopause or are still suffering from its symptoms. Coincident with the menopause some patients show an aggravation of their diabetic state and therefore require more insulin. Such women were chosen for this study in an attempt to ascertain the relationship between the hyperactivity of the anterior lobe of the pituitary gland during the menopause and the aggravation of the diabetes and to determine whether the inhibitory effect of estrogen might have a favorable effect on the diabetes. For the same purpose we selected some patients who were observed to be diabetic at about the time of the onset of the menopause. To test tne effect of estrogen when the menopause was not concerned, we included 2 patients who could not take insulin because of severe local reactions, presumably allergic, but who had no menopausal symptoms, to see what effect estrogen might have on diabetes in no way related to the menopause.

Thus there were four groups of patients: (1) those with a coincidental onset of diabetes and the menopause, (2) those whose diabetes was aggravated by the menopause, (3) those in whom the diabetes appeared long after the menopause and (4) those with no menopausal symptoms and presumptive allergic symptoms preventing the use of insulin.

REPORT OF CASES

1. DIABETES MELLITUS DISCOVERED AT ABOUT THE TIME OF ONSET OF THE MENOPAUSE

CASE 1.—Mrs. A. G., aged 50, came to the outpatient department of Lebanon Hospital because of pruritis vulvae, flushes and amenorrhea. Routine urinalysis revealed 2 per cent sugar, and the fasting blood sugar content was 360 mg. per hundred cubic centimeters. She was given a diet of carbohydrate 100 Gm., protein 71 Gm. and fat 70 Gm., with gradually increasing doses of protamine zinc insulin; but despite a final dose of 65 units daily she continued to show from 2 to 3 per cent sugar in her twenty-four hour specimen of urine. On Nov. 26, 1940 estrogen (2,000 rat units three times weekly) [14] was added to the regimen. The glycosuria rapidly cleared. The dose of insulin could then be rapidly reduced to 15 units daily. Eight months later the administration of estrogen was discontinued because of improvement in menopausal symptoms. The diabetic condition deteriorated, and the dose of insulin had to be increased to 35 units, although the diet was maintained as before. The results of two dextrose tolerance tests are here reproduced, one before the beginning of estrogen therapy and one before its cessation:

	Nov. 26, 1940		August 1941	
	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage
Fasting	400	6.5	211	0
½ hr. after administration of 100 Gm. of dextrose	500	5.5	274	Trace
1½ hr. after administration of 100 Gm. of dextrose	526	7.0	364	4
3 hr. after administration of 100 Gm. of dextrose	667	7.5	250	6.5

It will be noted that, while there was definite improvement in the condition of the patient and in the glycosuria, a definitely diabetic sugar curve persisted during estrogen therapy, although at a lower level.

14. The estrogens used were estradiol benzoate (dihydroxyestrin benzoate), furnished by the Schering Corporation, and estrone (ketohydroxyestrin), furnished by Endo Products, Inc., through Dr. A. B. Tamis, of our endocrine and gynecologic clinic. The doses of estradiol benzoate are expressed in rat units of estrogen and those of estrone in international units. Five or more international units was found to be the equivalent of 1 rat unit. The average dose of estrone contained 10,000 international units and that of estradiol benzoate 2,000 rat units. These were given three times weekly.

The general condition of this patient, including the weight and the subjective symptoms, seemed to parallel the improvement in the diabetic state.

CASE 2.—Mrs. J. M., aged 51, was discovered to have diabetes during a routine urinalysis July 6, 1937. Urinary sugar at that time amounted to 2.6 per cent, and the fasting blood sugar was 352 mg. per hundred cubic centimeters. Menopausal symptoms began at about the same time. The dextrose tolerance curve was as follows:

	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage
Fasting	352	2
½ hr.	500	2.5
1½ hr.	512	3
3 hr.	766	3.8

The patient was given a diet of carbohydrate 125 Gm., protein 74 Gm. and fat 77 Gm., with 15 units of protamine zinc insulin daily. This dose was later increased to 20 units, and the diabetes was satisfactorily controlled for several months. On Jan. 1, 1938 the glycosuria reappeared, the urinary sugar ranging from 1 to 2 per cent, with a fasting blood sugar of 286 mg. per hundred cubic centimeters. Because of marked flushes and other vasomotor symptoms she was given estrogen (10,000 international units) three times a week. The diet and the doses of insulin remained the same. This regimen was continued from February 1 to March 8. During this time the urine was sugar free. Several weeks after withdrawal of estrogen, glycosuria reappeared, with the urinary sugar ranging from 1.5 to 3 per cent, despite use of a diet containing less carbohydrate—carbohydrate 100 Gm., protein 71 Gm. and fat 70 Gm.—and an increase of insulin to 30 units daily. In August 1939 the dose was increased to 40 units daily, and the patient's urine became sugar free. This state lasted only a short time, and on Sept. 10, 1940, because of a return of glycosuria and aggravation of the menopausal symptoms, estrogen therapy was resumed, the diet and the insulin being kept at the same levels. The urinary sugar was soon reduced to 0.2 per cent and less, remaining at these levels despite the fact that the dose of insulin had to be reduced finally to 20 units daily because of hypoglycemic reactions. At about this time, too, an infection of the left foot developed, which healed promptly and was not accompanied by an aggravation of the diabetes. On Sept. 30, 1941 diethylstilbestrol, 1 mg. twice daily, was substituted for estrone, with about the same results, but its administration had to be discontinued in December because of profuse vaginal bleeding.

This patient showed a definitely beneficial effect on her diabetes from estrogen, with a lag in reestablishment of the condition after estrogen therapy was discontinued. A later administration of estrogen was again effective in improving the diabetic state.

CASE 3.—Mrs. S. W., aged 50, was discovered to have glycosuria Nov. 3, 1928. Urinary sugar at this time amounted to 3.5 per cent and blood sugar to 260 mg. per hundred cubic centimeters. Several months later the patient began to have flushes, menorrhagia, weakness, severe headaches and hypertension (blood pressure, 200 systolic and 100 diastolic). She was given a diet of carbohydrate 100 Gm., protein 71 Gm. and fat 70 Gm., and despite the administration of 45 and later 50 units of regular insulin daily there was no appreciable change in the diabetic state. Oral estrogen therapy was started June 11, 1939. This was also ineffective. Several weeks later parenteral estrogen therapy (injection of 20,000 international units three times weekly) was substituted. This was followed by such a marked reduction in the glycosuria that the dose of insulin had to be reduced to 10 units daily. During this regimen the urinary sugar was reduced, the content ranging occasionally up to 0.5 per cent.

Dextrose tolerance tests were done, the first before estrogen therapy and the latter after, with the following results:

	Nov. 14, 1938		Feb. 13, 1941	
	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage
Fasting	253	1.5	238	0.9
½ hr.	400	3.0	333	2.5
1½ hr.	500	3.5	345	0
3 hr.	334	4.0	206	0

The administration of estrogen was discontinued May 20, 1941 and the dose of insulin increased to 40 and later 50 units because of continued glycosuria. The glycosuria increased during the profuse menstrual periods. In general the diabetic condition paralleled the menopausal symptoms.

This patient's diabetes was difficult to control without parenteral administration of estrogen. Oral administration of diethylstilbestrol was ineffective.

CASE 4.—Mrs. A. A., aged 51, had had amenorrhea since January 1937. She was first seen by one of us (S. G.) on Feb. 25, 1938 because of diabetic symptoms, a urinary sugar content of 5 per cent and a blood sugar content of 550 mg. per hundred cubic centimeters. For the previous two months she had suffered with severe vasomotor menopausal symptoms, mainly flushes and attacks of faintness. She had attended the Mount Sinai Hospital diagnostic service four years previously, where examination had given essentially negative results except to show a slight tremor. The basal metabolic rate was then normal. A diet containing carbohydrate 99 Gm., protein 79 Gm. and fat 142 Gm. was prescribed, and the patient's husband, a physician, was asked to give her 2,000 rat units of estrogen parenterally twice weekly. On March 7 her urine was sugar free, and so her diet was increased to carbohydrate 125 Gm., protein 89 Gm. and fat 150 Gm., the use of estrogen being continued. The urine remained sugar free. The fasting blood sugar was 164 mg. per hundred cubic centimeters on March 14 and 154 mg. on March 28. On April 27 the urine was still sugar free, and the blood sugar was 113 mg. per hundred cubic centimeters. On April 29 the patient began to menstruate for the first time since January 1937. She did not menstruate after that, although estrogen was still given. On November 4 her urine was sugar free and she was taking practically a normal diet, even eating cake at times and drinking some beer. On April 18, 1939 her blood sugar was 148 mg. per hundred cubic centimeters. She has continued with estrogen, and her urine is sugar free unless estrogen is omitted, when glycosuria and menopausal symptoms reappear. She continues to take a practically unrestricted diet. In January 1942 oral administration of diethylstilbestrol was tried as a substitute for parenteral administration of estrogen, but this was ineffective in controlling glycosuria. A return to parenteral use of estrogen was again effective in controlling the diabetes.

This patient was never given insulin. From the start estrogen and diet were prescribed, and finally estrogen was given with a practically unrestricted diet and without insulin. Control of the diabetes, of the menopausal symptoms and of the general condition has been entirely satisfactory from Feb. 25, 1938 to the time of writing.

CASE 5.—Mrs. I. R., aged 55, was discovered to have diabetes in 1935; the condition was so severe that with a diet of carbohydrate 100 Gm., protein 71 Gm. and fat 70 Gm. she required 60 units of regular insulin daily for control. This was satisfactory for about one year, when glycosuria appeared, with 3 to 5 per cent sugar in the urine, together with traces of acetone, and a fasting blood sugar content of 460 mg. per hundred cubic centimeters. The amount of insulin had to be increased to 120 units daily, divided into four doses. On Sept. 3. 1940 the administration of estrogen was started in doses of 10,000 international units, later changed to 2,000 rat units, three times a week. Soon after this the dose of insulin was gradually reduced to 50 units of protamine zinc insulin and later to 35 units a day. With this regimen, the urinary sugar was maintained at about 1 per cent, with an occasional rise to 2 per cent. Dextrose tolerance tests gave the following results:

	Oct. 15, 1940		July 29, 1941	
	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage
Fasting	385	6	286	1.7
½ hr.	500	7	420	2.5
1 hr.	587	7.5	410	5
2 hr.	665	7.5	364	5

After the onset of the menopause this patient had rather severe diabetes which was favorably influenced by estrogen therapy, although not as completely as in some of the other cases.

CASE 6.—Mrs. R. S., aged 52, came to our diabetic clinic in March 1935. Her diabetes had been discovered several months before in another hospital, where she received a dose of 20 units of insulin daily in addition to a diet of 1,600 calories. Her complaints were loss of weight of about 10 pounds (4.5 Kg.) in one year, irregularity of the menstrual periods of six months' duration and nervousness, melancholia and flushes of increasing frequency. Determination of the urinary sugar and the fasting blood sugar on March 5, 1935 revealed 4.3 per cent and 192 mg. per hundred cubic centimeters, respectively. She was given a diet of carbohydrate 100 Gm., protein 70 Gm. and fat 70 Gm. and doses of insulin gradually increasing from 20 units to a maximum of 30 units, in two doses, daily. The patient was at all times uncooperative and often confessed to nonadherence to the diet and to omission of insulin. In spite of this she gained several pounds and the urinary sugar content came down to about 1 to 1.5 per cent. Because of the menopausal syndrome she was in the care of our endocrine department, where she was at first treated with sedatives, but in March 1937 her vasomotor disturbances became more pronounced and the urinary sugar rose until it reached a level of 3 per cent in a twenty-four hour specimen. Administration of estrogen, 10,000 international units, increased within a few weeks to 20,000 international units, three times weekly, was instituted on June 5. Insulin was withdrawn at the same time but had to be replaced in the regimen because of the glycosuria. She received estrogen for two years, until October 1939, during which she seldom needed more than 15 units to control her diabetes. The fasting blood sugar level on July 1, 1937

Results of Dextrose Tolerance Tests

Date	Results of Tests for Sugar	Fasting	Time After Dextrose ½ Hr.	1½ Hr.	2 Hr.	3 Hr.
September 1937	Blood (per 100 cc.)	185 mg.	266 mg.	328 mg.	.....	287 mg.
	Urine	Trace	0.8%	7.5%	.....	8.9%
Nov. 6, 1937	Blood (per 100 cc.)	182 mg.	235 mg.	312 mg.	333 mg.	.....
	Urine	Trace	Trace	2.0%	2.5%	.....
Jan. 13, 1938	Blood (per 100 cc.)	222 mg.	286 mg.	303 mg.	.....	308 mg.
	Urine	0	1.0%	2.5%	.....	3.0%
Feb. 1, 1938	Blood (per 100 cc.)	175 mg.	235 mg.	333 mg.	.....	364 mg.
	Urine	0	Trace	3.0%	.....	3.2%
April 13, 1939	Blood (per 100 cc.)	174 mg.	260 mg.	274 mg.	.....	256 mg.
	Urine	0	0	2.5%	.....	2.5%
April 10, 1940	Blood (per 100 cc.)	110 mg.	191 mg.	156 mg.	.....	133 mg.
	Urine	0	Trace	Faint trace	.....	0
Feb. 6, 1941	Blood (per 100 cc.)	111 mg.	191 mg.	167 mg.	.....	98 mg.
	Urine	0	0	0	.....	0

was 191 mg. per hundred cubic centimeters. On Oct. 21, 1939 parenteral administration of estrogen was replaced by diethylstilbestrol therapy, 1 mg. being given daily. The latter apparently controlled the vasomotor disturbances of the menopause but not the diabetes, because there was soon a return of glycosuria, with 1.5 to 2 per cent of urinary sugar. On Nov. 14, 1940 administration of estrogen in doses of 10,000 international units was resumed, and it was continued for several months; during estrogen therapy the urinary sugar never rose above 0.5 per cent. The patient refused to submit to a dextrose tolerance test.

CASE 7.—Mrs. L. F., aged 47, was discovered to have sugar in the urine in 1939 in a routine urinalysis. At that time she complained of the sudden onset of irregularity and profuseness of the menstrual flow, flushes and nervousness. The blood sugar was 300 mg. per hundred cubic centimeters and the urinary sugar 2.8 per cent. At first a low caloric diet relatively high in carbohydrates and amounting to about 1,600 calories per day controlled the diabetes and reduced the urinary sugar to about 1 per cent. From the onset the patient refused to take insulin. In December 1940 the glycosuria increased, and at that time the blood sugar content was 333 mg. per hundred cubic centimeters. Diethylstilbestrol, 5 mg. daily, in addition to the aforementioned diet was tried, with no apparent improvement in the glycosuria, the urinary sugar ranging from 2 to 3 per cent. Estrogen, 2,000 rat units three times a week, was substituted, and within two weeks the urine became sugar free, and it remained so except for occasional rises to about 0.5 per cent.

This patient had a good response to estrogen given parenterally but not orally.

CASE 8.—Mrs. S. R., aged 50, came to the outpatient department in 1937 because of irregularity of menstrual periods, weakness, nervousness, irritability and a progressive gain in weight. At that time there was 2.5 per cent sugar in the urine and the fasting blood sugar was 185 mg. per hundred cubic centimeters. She was given a diet of carbohydrate 125 Gm., protein 71 Gm. and fat 70 Gm., and from September 7 was given 10,000 international units of estrogen three times a week. She refused to take insulin. Estrogen therapy was continued until February 1939. During this period the urine was sugar free with few exceptions and the sugar tolerance curve gradually returned to an approximate normal. The results of dextrose tolerance tests are shown in the table.

This patient responded rather well to estrogen therapy and diet without the use of insulin. The dextrose tolerance curves paralleled the improvement in the glycosuria. This did not always happen in patients who showed improvement.

2. DIABETES AGGRAVATED BY THE MENOPAUSE

CASE 9.—Mrs. A. L., aged 47, was discovered to have diabetes in 1937, and from then until 1940 she received 10 units of insulin daily and a diet of carbohydrate 100 Gm., protein 71 Gm. and fat 70 Gm. This treatment controlled her diabetic condition. The urinary sugar was reduced from 3 to 0.5 per cent or none, and the results of repeated tests of the fasting blood sugar ranged between 250 and 161 mg. per hundred cubic centimeters. The level March 15, 1937 was 170 mg. The patient continued on this regimen until 1940, when she began to have flushes, became irritable, experienced attacks of palpitation and noticed a periodic irregularity and relative scantiness in the menstrual flow. Concomitantly the urinary sugar rose to 2.5 per cent and the fasting blood sugar to 199 mg. per hundred cubic centimeters, and a month later the latter was 250 mg. Because of the patient's refusal to take additional injections she was given 5 mg. of diethylstilbestrol orally daily. Within one week the glycosuria disappeared and the fasting level of blood sugar dropped to 130 mg. per hundred cubic centimeters. There were no unpleasant reactions to diethylstilbestrol, but because of the patient's failure to cooperate no dextrose tolerance tests were performed. She discontinued treatment against our advice in November 1940, because of nausea, but when her climacteric symptoms and glycosuria reappeared a short time later she resumed it until July 1941 with good results. At the time of writing she still refuses parenteral estrogen therapy.

This patient is the only one in the group who seemed to benefit from diethylstilbestrol, given orally.

CASE 10.—Mrs. M. W., aged 59, was discovered to have diabetes nine years ago. Then the urinary sugar was 2 per cent and the blood sugar 217 mg. per hundred cubic centimeters. A diet of carbohydrate 100 Gm., protein 71 Gm. and fat 70 Gm. was sufficient to render the urine sugar free and reduce the blood sugar to 154 mg. per hundred cubic centimeters.

In 1938, about the time of the onset of the menopause, the sugar content of the urine rose to 3 per cent. Estrogen therapy was begun on October 18 and discontinued May 28, 1941 (10,000 international units three times a week). During the entire period of estrogen therapy the urine was sugar free and the blood sugar never rose above 80 mg. per hundred cubic centimeters. The patient refused to take insulin. After cessation of the estrogen therapy glycosuria reappeared (1 to 3 per cent of urinary sugar) and the fasting blood sugar ranged between 160 and 180 mg. per hundred cubic centimeters.

This patient whose diabetes was aggravated by the menopause refused insulin but responded well to treatment with estrogen and diet alone.

3. DIABETES APPEARING LONG AFTER THE MENOPAUSE

CASE 11.—Mrs. L. K., aged 53, whose menopause began in 1926, was discovered to have diabetes at the clinic of Mount Sinai Hospital in 1929. Up to March 4, 1940 a diet of carbohydrate 100 Gm., protein 65 Gm. and fat 60 Gm. controlled her diabetes, but after that glycosuria developed in spite of the diet. In September 1940 her blood sugar amounted to 286 mg. per hundred cubic centimeters and her urinary sugar to 1 per cent. Diethylstilbestrol was given for several weeks, with no apparent improvement in the glycosuria. The substitution of insulin, at first 10 and then 15 units daily, is controlling her diabetic state at the time of writing. The blood sugar on Feb. 2, 1941 was 140 mg. per hundred cubic centimeters, and since then her condition has not changed appreciably. No estrogen was used parenterally.

The diabetes of this patient was discovered three years after the menopause, and that was thirteen years before her appearance at our clinic. Diethylstilbestrol failed to influence her diabetes.

CASE 12.—A. LoB., aged 59, came to our clinic on Sept. 12, 1939, after the discovery of 4 per cent sugar in the urine and a fasting blood sugar content of 222 mg. per hundred cubic centimeters. At first a diet of carbohydrate 100 Gm., protein 71 Gm. and fat 75 Gm. and 25 units of protamine zinc insulin controlled the diabetes, and she gained several pounds. Within two months after the institution of this regimen the glycosuria returned and could be controlled only by 40 units of protamine zinc insulin or more daily. Estrogen, 10,000 international units given three times weekly, was tried, in addition to the original 25 units of insulin, and was administered from August 27 until December 1940, when, because of no change in the diabetic condition, estrogen was withdrawn and the insulin increased to 35 units daily. At present the patient receives 40 units of protamine zinc insulin once daily, with fairly good results, the urinary sugar never reaching 1 per cent.

CASE 13.—Mrs. R. S., aged 65, had had diabetes of ten years' duration. She had passed through the menopause twenty-five years before. In spite of her obesity and myxedematous appearance, the basal metabolic rate on three different occasions was + 31, + 40 and + 22 per cent, respectively. She had a marked polyuria, excreting 128 ounces (3,800 cc.) or more of urine daily. The urine continued to have a low specific gravity. The polyuria could be controlled only with pitressin. The diabetes was controlled with 20 to 30 units of insulin daily and a diet of carbohydrate 125 Gm., protein 70 Gm. and fat 70 Gm. A dextrose tolerance test on Jan. 8, 1935 gave the following results:

Fasting	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Percentage
	154	0
½ Hr.	323	0
1 Hr.	362	0
2½ Hrs.	328	0

The fasting blood sugar level on March 24, 1937 and on May 4, 1938 was 240 mg. and 200 mg. per hundred cubic centimeters, respectively, in spite of the persistent absence of sugar in the urine. At that time roentgen examination of the head was undertaken, and the report reads, "Destruction of posterior clinoid processes due very likely to tumor" (Dr. S. F. Weitzner). In 1940 sugar began to appear in the urine and persisted, in spite of an increase in the dose of insulin to 50 units daily. On February 20 estrogen therapy was added, 10,000 international units being given three times weekly. During this therapy the patient's urine remained sugar free, but, because of the return of polyuria, pitressin had frequently to be substituted for the estrogen, as the patient refused to take both. With the return to administration of the former the polyuria subsided but the glycosuria recurred. The patient was particularly anxious to receive pitressin and begged for it at each clinical session. This was because she dribbled urine even on the street when the polyuria was severe.

The diabetes of this patient appeared years after the menopause but might have been related to the evident pituitary disease and therefore responsive to estrogen.

4. DIABETES UNRELATED TO THE MENOPAUSE AND ALLERGY (?) TO INSULIN

CASE 14.—Mrs. B. S., aged 52, had had diabetes for many years. Until four years earlier this had been controlled by a diet of carbohydrate 105 Gm., protein 60 Gm. and fat 60 Gm. Then 25 units of insulin daily had to be added, although the patient continued to adhere to her diet. However, soon after the institution of insulin therapy its use was discontinued because of the generalized pruritus that followed each injection and the severe local reactions at the site of the injection. The allergy clinic found marked sensitivity to pork. Crystalline insulin produced the same reaction. Estrogen was tried because of the difficulty in controlling the diabetes by diet alone. This was given for eight months. The glycosuria was never appreciably reduced.

CASE 15.—Mrs. D. W., aged 47, was discovered to have diabetes five years before and had so far been without vasomotor menopausal disturbances. Her reactions to insulin were similar to those in case 14, and estrogen was tried and again found disappointing.

Neither of these patients had menopausal symptoms; they were chosen for treatment because insulin could not be used. Estrogen was tried but had no effect on the diabetes.

COMMENT

As the literature on the treatment of diabetes with estrogenic hormone has been so contradictory, it was felt that an effort should be made to select the proper patient for such treatment. It was for this reason that our patients were divided into the following four groups: (1) those in whom the onset of diabetes coincided with that of the menopause, (2) those in whom existing diabetes was aggravated by the menopause, (3) those in whom the diabetes appeared long after the menopause and (4) 2 who had had no menopausal symptoms but who could not take insulin because of severe local reactions, presumably allergic.

Thus, of our 15 patients 8 had a concomitant onset of diabetes and the menopause, 2 had diabetes aggravated by the menopause and in 3 diabetes appeared long after the menopause. The 2 patients whose existing diabetes was aggravated by the onset of the menopause were of particular interest because they demonstrated the effect of estrogen on diabetes aggravated by this phase of pituitary activity in contradistinction to that which has developed some years after the menopause and therefore presumably in the quiescent phase of the anterior lobe of pituitary gland. Patient 13 is of separate interest because she was intensively studied for several years from the standpoint of concomitant diabetes mellitus and diabetes insipidus. She had extreme polyuria which did not parallel the grade of her glycosuria and which, indeed, antedated her diabetes. When her urine was sugar free and she was still having polyuria, the specific gravity of her urine was much below 1.010, usually 1.002 to 1.004. Control of the polyuria was obtained readily with pitressin, although this would be expected to increase glycosuria and with it polyuria.

The patients with concomitant diabetes and the menopause all responded favorably to estrogen, as well as those with aggravation of diabetes at the time of the menopause. Patient 13, whose diabetes came on long after the menopause, was also benefited, because she had definite pituitary disease. The other 2 patients with onset of diabetes long after the menopause were not thus benefited. The two allergic patients, too, showed no response to estrogen therapy.

The diagnosis of the menopause was assumed on the basis of subjective complaints, such as headaches, flushes, palpitation, emotional instability, perspiration, vague muscle pain and disturbances of the menstrual rhythm.

Throughout the period of study a pragmatic course was followed and the results were gaged from analysis of the urine and blood and observation of the general condition and weight of the patient. No patient was exposed to lack of control of her diabetes by use of insufficient insulin. The elimination of insulin was accomplished gradually.

Our findings agree with those of Mazer and Israel that the glycosuria and hyperglycemia can be controlled only by large doses of estrogen. Only 1 patient received 30,000 international units of estrogen weekly. The others required from 60,000 to 80,000. The response to estrogen was the same with estrone (ketohydroxyestrin) and estradiol benzoate (dihydroxyestrin benzoate) provided large doses were given.

Improvement in the diabetes closely paralleled that of the menopausal symptoms. Subjective improvement was always accompanied by marked reduction of glycosuria and hyperglycemia. The urine frequently became sugar free.

Our experience with diethylstilbestrol given by mouth was limited because of the recent introduction of this substance for clinical trial, but if one judges from the scanty available data its effect on hyperglycemia does not parallel its effect on menopausal symptoms. It would be interesting to compare the effect of oral

and of parenteral administration. Mazer, Israel and Ravetz [15] have recently reported their observations on the parenteral use of diethylstilbestrol. They found its effect the same as that of estrogen.

There remains the broad question as to what patients may be treated with estrogen. Can we say that the patient who has severe climacteric symptoms and diabetes is the one, or shall we conclude that the suitable patient is the one whose diabetes comes on at about the same time as the menopause? This work with a limited number of subjects rather indicates that the proper patients for this treatment are those in whom diabetes develops at about the same time as the menopause or those with aggravation of diabetes at this period. Careful work at various clinics will clarify this question.

In conclusion it must be stated that treatment of diabetes with estrogen must not be lightly undertaken. It must be carried out only by physicians with a thorough knowledge of the problems involved, and with careful observation of the patient. It should not be generally undertaken until all the problems concerned with its use have been solved.

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15. Mazer, C.; Israel, S. L., and Ravetz, E.: The Synthetic Estrogen Stilbestrol, J. A. M. A. **116**:675-681 (Feb. 22) 1941.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Concluded from Page 145)

SPLENIC DISORDERS

Banti's Syndrome.—An instance of Banti's disease due to stenosis of the portal vein without hepatic cirrhosis is reported by Trimble and Hill.[318] The postmortem observation of mechanical congestive splenomegaly lends further support to the view of Thompson that hypertension of the portal vein is the common denominator of so-called Banti's disease. The portal hypertension results in splenomegaly, collateral circulation and the development of esophageal varices. Churchill [319] cites a 24 year old man who had ascites, anemia, leukopenia, thrombopenia and splenomegaly. Splenectomy was performed, and the patient died with bronchopneumonia during the postoperative period. The spleen was shown to contain increased amounts of fibrous tissue and the splenic vein hyalinized plaques of intimal thickening. Pemberton [320] reports the outcome in 226 cases in which splenectomy was performed at the Mayo Clinic for splenic anemia and Banti's disease. The mortality rate for the operation was 12.4 per cent. The survival period was as follows: five years in 55.1 per cent of the cases; ten years in 43.2 per cent, twenty years in 22.7 per cent. Fully 50 per cent of the patients who experienced gastrointestinal hemorrhages before operation had recurrence of hemorrhages after operation. The deaths of one third of the patients were directly attributable to hemorrhages.

An increased number of target cells in the blood of dogs and guinea pigs was observed by Miller, Singer and Dameshek [321] after removal of the spleen and after either incomplete or complete ligation of the splenic vein. The greatest number of target cells were seen in dogs after splenectomy and the fewest after incomplete ligation of the splenic vein. No target cells were noted, although Howell-Jolly bodies were present, in rabbits' blood after splenectomy. The relationship of the spleen to the morphologic picture of blood regeneration was the subject of

318. Trimble, W. K., and Hill, J. H.: Congestive Splenomegaly (Banti's Disease) Due to Portal Stenosis Without Hepatic Cirrhosis; Aneurysms of the Splenic Artery: Report of a Case with Necropsy, Arch. Path. **34**:423 (Aug.) 1942.

319. Churchill, T. P.: Banti's Syndrome, Texas State J. Med. **37**:720, 1942.

320. Pemberton, J. deJ.: The Present Status of Surgery of the Spleen, Cincinnati J. Med. **22**:564, 1942.

321. Miller, E. B.; Singer, K., and Dameshek, W.: Experimental Production of Target Cells by Splenectomy and Interference with Splenic Circulation, Proc. Soc. Exper. Biol. & Med. **49**:42, 1942.

a study by Cruz and Robscheit-Robbins.[322] The spleens were removed from dogs, which later were made anemic either by the administration of acetylphenylhydrazine or by hemorrhage. The normoblastic response of the splenectomized animals during the initial phase of the regeneration of the blood was four times as great as that observed in normal dogs, and primitive erythroblasts were found in much greater numbers. The authors suggest a relation between the function of the spleen and either the maturation of erythroblasts in the marrow or the release of new red blood cells into the circulation.

Gaucher's Disease.—An instance of Gaucher's disease with hemolytic anemia and thrombopenia is reported by Mandelbaum, Berger and Lederer.[138] The spleen, weighing 6,822 Gm., was removed at operation, and subsequently the blood values rose to normal. No Gaucher cells were found in the bone marrow. Lipid analysis of this spleen was undertaken by Sobel and Kaye.[323] The characteristic lipid constituent, kerasin, was isolated and identified, and an increase of the cerebrosides at the expense of neutral fat was found. Danielson, Hall and Everett[324] report the isolation of a kerasin-like cerebroside containing d-dextrose rather than d-galactose from the spleen of a 4 year old girl with Gaucher's disease. The authors point out that their finding and others recently reported suggest that the synthesis of a glucoside type of splenic kerasin is a frequent occurrence in this disease.

Emanuel[325] stresses the diagnostic value of aspirated sternal marrow in suspected cases of Gaucher's disease. The characteristic large Gaucher cells were found by the author in the marrow of 2 men aged 30 and 35 years, respectively. The platelet count was depressed and the coagulation time was prolonged in both cases. Transient leukocytosis, the white blood cell count attaining 50,000 per cubic millimeter, was noted in 1 case. Gaucher cells were found on biopsy of a suspected lesion of bone by Reed and Sosman.[326] Myer[327] reports the postmortem observations in a 7 year old child with Gaucher's disease. The mediastinal and hilar glands were enlarged and contained masses of the pathognomonic cells. During life a severe productive cough had been noted, and necropsy revealed extensive invasion of the lungs by the disease process. Reisman and Utz[328] were unable to find Gaucher cells in the sternal marrow of a 10 year old girl with the disease, but the typical cells were seen in splenic tissue obtained by puncture of the spleen. Rapid increase in the size of this organ eventually led to splenectomy, but the bone lesions, characteristic of the disease, continued to progress.

HEMORRHAGIC DISORDERS AND BLOOD COAGULATION

General Observations.—Classifications of the hemorrhagic diseases are presented by Lozner,[329] Jurgens[330] and Dam.[331] The diagnosis, the clinical manifes-

322. Cruz, W. O., and Robscheit-Robbins, F. S.: Relationship Between the Spleen and the Morphologic Picture of Blood Regeneration, Am. J. M. Sc. **203**:28, 1942.

323. Sobel, A. E., and Kaye, I. A.: Gaucher's Disease: A Case with Hemolytic Anemia and Marked Thrombopenia; Improvement After Removal of Spleen Weighing 6,822 Grams; Lipid Analysis of the Gaucher's Spleen, Ann. Int. Med. **16**:446, 1942.

324. Danielson, I. S.; Hall, C. H., and Everett, M. R.: Glucoside Type of Cerebroside in the Spleen in Gaucher's Disease, Proc. Soc. Exper. Biol. & Med. **49**:569, 1942.

325. Emanuel, E.: Gaucher's Disease: Report of Two Unrelated Cases, Edinburgh M. J. **48**:843, 1941.

326. Reed, J., and Sosman, M. C.: Gaucher's Disease, Radiology **38**:579, 1942.

327. Myer, B.: Gaucher's Disease of the Lungs, Brit. J. Child. Dis. **38**:135, 1941.

328. Reisman, H. A., and Utz, D. W.: Gaucher's Disease: Report of Case, Arch. Pediat. **59**:446, 1942.

329. Lozner, E. L.: Hemorrhage and Hemorrhagic Diathesis, U. S. Nav. M. Bull. **40**: 641, 1942.

(Footnotes continued on next page)

tations and the treatment of these conditions are covered by Pepin and collaborators [332] and by Lessard.[333] Kugelmass [334] outlines the clinical characteristics and discusses the treatment of the hemorrhagic diseases as encountered in children.

The role of vitamins in the hemorrhagic states is discussed by Scarborough.[335] Vitamin D has been shown to reduce the bleeding time in jaundiced patients when the Ivy method is employed. This vitamin is also thought to influence the formation of clot. Vitamin C rapidly controls the hemorrhagic manifestation in scurvy, but earlier reports that it exerted a beneficial effect in thrombopenic purpura have received little recent confirmation. Dam [331] reports that chicks on a diet deficient in vitamin E had accumulations of plasma under the skin. Except for alphatocopherol, all known vitamins, including eriodictin and hesperidin, in which vitamin P is thought to reside, proved ineffective in protecting against the disease.

Essential Thrombopenic Purpura.—The occurrence of an acute form of thrombopenic purpura which differed from the usual essential type of the disease by rapid progression, presence of icterus, cerebral manifestations and failure to respond to transfusions or splenectomy is reported by Altschule [336] in a 50 year old woman with terminal manifestations of intracranial disease, icterus, rapidly progressive anemia, purpura and fever. Transfusions and splenectomy did not arrest the process, and necropsy revealed a large number of thrombotic lesions made up of masses of platelets within the capillaries and to a lesser extent within the arterioles. The cause of the change in the vascular endothelium resulting in the deposition of platelets is not known. It is suggested that the profound thrombopenia seen in this type of purpura may be due to withdrawal of enormous numbers of platelets from the circulation. That a similar phenomenon occurs in other forms of thrombopenia, but in a less easily detected form, is suggested by the author.

Whitney and Barritt,[337] reviewing the literature, found 14 reported cases of congenital thrombopenic purpura, to which they add 2 new cases. The first child, born to a mother who had undergone splenectomy for thrombopenic purpura twelve years prior to her pregnancy, was covered with purpuric spots at birth and died on the third day of life. A platelet count of 80,000 per cubic millimeter, a bleeding time of one and one-half minutes and a coagulation time of three and one-half minutes were recorded. A second pregnancy ensued, and this infant likewise showed petechiae at birth. The platelet count was 90,000 per cubic millimeter, and the bleeding time was eleven minutes and the coagulation time one and one-half minutes, and the prothrombin value was 28 per cent of normal.

330. Jurgens, R.: Systematik der hämorrhagischen Diathesen, Schweiz. med. Wchnschr. **71**:1494, 1941.

331. Dam, H.: Factors in Preventing the Blood from Leaving the Vascular System, Quart. Bull. Indiana Univ. M. Center **3**:43, 1942.

332. Pepin, J. R.; Lefebvre, R.; Dandurand, R., and Dussault, R.: Les grands syndromes hémorrhagiques, Union méd. du Canada **71**:251, 1942.

333. Lessard, R.: Symposium on the Hemorrhagic Syndromes: The Hemorrhage from Blood Dyscrasia, Union méd. du Canada **71**:1267, 1942.

334. Kugelmass, I. N.: Hemorrhagic Problems in Child Surgery, Am. J. Clin. Path. **12**:467, 1942.

335. Scarborough, H., in Discussion on Vitamins and Hæmorrhagic States, Proc. Roy. Soc. Med. **35**:407, 1942.

336. Altschule, M. D.: A Rare Type of Acute Thrombocytopenic Purpura: Widespread Formation of Platelet Thrombi in Capillaries, New England J. Med. **227**:477, 1942.

337. Whitney, L. H., and Barritt, A. S.: Spontaneous and Hereditary Thrombopenic Purpura in a Mother and Two Sons, Am. J. Dis. Child. **64**:705 (Oct.) 1942.

Despite blood transfusion and the administration of vitamin K, this child succumbed twenty-four hours after birth. Postmortem examinations were made on both infants.

Urbanski and Hutner [338] observed a mother with chronic thrombopenic purpura whose first pregnancy terminated in the birth of a stillborn child. The infant was covered with petechial hemorrhages, and at necropsy there were seen extensive subarachnoid, subpleural and subpericardial hemorrhages. On the nineteenth postpartum day, profuse vaginal bleeding commenced, which necessitated splenectomy. The mother made an uneventful clinical recovery, although no platelet counts of over 100,000 per cubic millimeter were recorded during a two year follow-up period. A second pregnancy ensued two and a half years after the removal of the spleen. The infant showed petechiae on the face and on the buccal membranes at birth and had a bleeding time of five and one-half minutes and a platelet count of 23,000 per cubic millimeter. The petechiae rapidly disappeared, and the infant developed normally. The mother had a normal postpartum course and subsequently underwent two further pregnancies, with normal infants in each instance.

The spleen was removed in 11 cases of chronic idiopathic purpura by Phillips and Zionts.[339] One patient died; another was alive eight months postoperatively, but the hemorrhagic tendency was unaltered; the remaining 9 patients showed complete cure. Acute thrombopenia was observed in 5 patients, with recovery following transfusions in 4 and a fatal termination in the fifth. Splenectomy was not done if the disease was in an acute form. The importance of making careful diagnostic studies before splenectomy, to rule out symptomatic purpura, is stressed.

Evans [340] reports successful arrest of acute hemorrhagic thrombopenic purpura following splenectomy. Taylor [341] calls attention to instances of purpura haemorrhagica in which severe and protracted menorrhagia is the only clinical manifestation of the disease.

Ligation of the splenic artery for thrombopenic purpura is discussed by Berg and Rosenthal,[342] who tried the procedure in 2 cases, without any hematologic and only transient clinical improvement resulting. Splenectomy was necessitated in both instances because of the return of symptoms. One case terminated fatally.

Wiseman and Doan [343] call attention to the syndrome which they named primary splenic neutropenia. The underlying etiologic factor is said to be a hypersplenic state wherein the function of the spleen in destroying abnormal or senile cells is augmented by pathologic destruction of normal elements. Such a mechanism is suggested as responsible for thrombopenic purpura as well as for congenital hemolytic icterus and splenic neutropenia, with, in each instance, selective pathologic phagocytosis of a specific cellular element.

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338. Urbanski, A. X., and Hutner, C. I.: Thrombopenic Purpura Complicating Pregnancy: Treatment by Splenectomy Resulting in Clinical Cure and Followed by Three Full Term Pregnancies, J. A. M. A. **120**:754 (Nov. 7) 1942.

339. Phillips, J. R., and Zionts, M. A.: Thrombocytopenic Purpura, Am. J. Surg. **57**:51, 1942.

340. Evans, R. L.: Splenectomy in Thrombocytopenic Purpura, Guthrie Clin. Bull. **12**:56, 1942.

341. Taylor, W. W.: Thrombocytopenic Purpura as a Cause of Uterine Bleeding, Memphis M. J. **17**:182, 1942.

342. Berg, A. A., and Rosenthal, N.: Ligation of the Splenic Artery for Thrombocytopenic Purpura and Congestive Splenomegaly, J. Mt. Sinai Hosp. **8**:382, 1942.

343. Wiseman, B. K., and Doan, C. A.: Primary Splenic Neutropenia: A Newly Recognized Syndrome, Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura, Ann. Int. Med. **16**:1097, 1942.

Studies of the action of extracts from the spleens of patients with thrombopenic purpura on the platelets and hemopoietic organs of rabbits are reported by Paul.[344] Extracts of five spleens were prepared according to the method of Troland and Lee and were given to the rabbits by vein. A transient fall in the platelet count was observed eight hours after the injection, followed by a return to the preinjection level within twenty-four hours. Bone marrow sections and imprints revealed no significant change in the number of the megakaryocytes or in their structure.

Uihlein[345] likewise failed to demonstrate clearly or to deny definitely the presence of a thrombocytolytic substance in acetone extracts of spleens removed from patients with idiopathic thrombopenic purpura. Of 13 such splenic extracts administered intravenously to rats, 2 produced a considerable drop and 3 a moderate decrease in the number of circulating platelets. Of extracts from the spleens of 5 patients with hemolytic icterus, only 1 produced a decrease in platelet count. This response was consistent in all animals treated, and the active principle was not destroyed by heat. In all, 28 extracts were prepared, including 4 from normal spleens, 1 from liver and 1 from some lymph tissue as control material. Twenty-two extracts failed to produce significant thrombopenia, but all animals appeared apathetic for short periods after receiving an injection. Because of the inconsistency of the results, the author feels that a new method of extraction of "thrombocytopen" is essential before any final conclusion can be made.

Secondary Thrombopenic Purpura.—A case of thrombopenic purpura secondary to carcinomatous replacement of the bone marrow is reported by Willis.[346] The primary site of the neoplasm was the stomach. Fifteen other instances of carcinoma of the stomach associated with secondary thrombopenic purpura were collected from the literature. Often the carcinoma was not discovered until autopsy.

Thrombopenic purpura following the administration of sulfathiazole is reported by two authors. Rosenfeld and Feldman[347] observed profuse bleeding from the nose and the mouth, hematuria and extensive petechiae in a 37 year old man after 5.5 Gm. of sulfathiazole had been administered during a three day period. The platelet count declined to 2,000 per cubic millimeter; the bleeding time was six minutes. Following withdrawal of the drug there were prompt recovery and return of the platelet count to normal, and two weeks later 15 Gm. of sulfathiazole was given in a five day period without recurrence of purpura. Werner[348] reports thrombopenic purpura following sulfathiazole in a 16 year old boy. This patient received 13.9 Gm. of sulfathiazole during a period of seven days, with the appearance of a slight rash on the fifth day. An uneventful recovery from the infection of the upper respiratory tract followed. Six weeks later 1.0 Gm. of sulfathiazole was administered, and within twelve hours purpura and gingival bleeding developed. The platelets disappeared from the blood, and a bleeding time of thirty-five minutes was recorded. Conservative therapy, without specific measures, resulted in complete recovery.

344. Paul, J. T.: Effect of Splenic Extracts from Cases of Essential Thrombocytopenic Purpura on the Platelets and Hematopoietic Organs of Rabbits, J. Lab. & Clin. Med. **27**: 754, 1942.

345. Uihlein, A.: Effect of Injection of Tissue Extracts on the Number of Blood Platelets, J. Lab. & Clin. Med. **28**:157, 1942.

346. Willis, W. H.: Thrombocytopenic Purpura and Carcinoma of Stomach: Report of a Case with Purpura Appearing After Subtotal Gastrectomy, Ann. Int. Med. **16**:782, 1942.

347. Rosenfeld, S., and Feldman, F.: Thrombocytopenic Purpura Due to Sulfathiazole, J. A. M. A. **118**:974 (March 21) 1942.

348. Werner, W. I.: Thrombocytopenic Purpura Following Administration of Sulfathiazole: Case Report, Southwestern Med. **26**:49, 1942.

Sulfadiazine caused acute thrombopenic purpura in a patient seen by Whitehouse and Watkins.[349] A 37 year old man with a pulmonary abscess had received an earlier course of sulfathiazole. Sulfadiazine was instituted in three short courses, and after the second there developed thrombopenia and bleeding from the gums. After recovery, four and one-half weeks later, a third course of sulfadiazine was begun. The ingestion of 7 Gm. in forty-eight hours caused the platelet count to drop from a normal level to 138,000 per cubic millimeter. The administration of the drug was discontinued, and no further hematologic phenomena developed.

Varas [350] reports the case of a 4 year old child with malaria in whom hemorrhagic purpura developed following the administration of 16.5 Gm. of quinine. An instance of thrombopenic purpura complicating antisyphilitic arsphenamine therapy is reported by Laird.[351] Graeber [352] presents 3 cases of thrombopenic purpura following the ingestion of sedormid (allylisopropylacetylcarbamide). The literature is briefly reviewed, and 15 additional cases are tabulated. Thiell [353] observed a case following the administration of sedormid and another following the administration of saridon, an anesthetic containing sedormid. Infectious mononucleosis associated with acute thrombopenic purpura was seen by Magner and Brooks.[214] The sternal marrow was studied in 10 patients by Moeschlin [354] during experimental tolerance tests with sedormid. A slight change to younger forms developed in the megakaryocyte series immediately after the development of acute thrombopenia. Two or three days later a progressive increase in the blood platelets was noted in the peripheral blood, consisting of pathologic and large forms. In hypersensitive patients sedormid produced thrombopenia in from thirty to sixty minutes. The author failed to demonstrate a lysin for platelets as a feature of acute thrombopenia.

Nonthrombopenic Purpura.—Barnes and Duncan [355] report a case of nonthrombopenic purpura with involvement of viscera, skin and joints. Laparotomy was done before the diagnosis was apparent. The ileum was seen to be greatly congested, with many subperitoneal hemorrhages, suggesting regional ileitis. The patient recovered. An instance of Henoch's purpura was reported by Quirno Lavalle and Mallo Huergo.[356] Looper [357] observed a 31 year old man who died with profuse pulmonary hemorrhages. Except for hematuria, no other evidence of a tendency toward bleeding was present. The platelet count was 712,800 per cubic millimeter. Necropsy showed evidence of purpura in the lungs, with no other abnormality present to account for the fatal bleeding.

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349. Whitehouse, F. R., and Watkins, C. H.: Acute Thrombocytopenic Purpura Following Sulfadiazine Therapy: Report of Case, Proc. Staff Meet., Mayo Clin. **17**:140, 1942.

350. Varas, R. P.: Hemorrhagic Purpura from Quinine Poisoning, Bol. Soc. cubana de pediat. **14**:49, 1942.

351. Laird, S. M.: Thrombocytopenic Purpura Complicating Arsenobenzene Therapy, Brit. M. J. **1**:381, 1942.

352. Graeber, W.: Thrombopenische Blutungen nach Sedormedgebrachs, München. med. Wchnschr. **89**:122, 1943.

353. Thiell, W.: Akute thrombopenische Purpura nach Sedormid-und Saridongebrach, München. med. Wchnschr. **89**:934, 1942.

354. Moeschlin, S.: Die Sedormid-Thrombozytopenie anhand von Sternalpunktaten, Belastungs- und Transfusions-versuchen, Schweiz. med. Wchnschr. **72**:119, 1942.

355. Barnes, C. G., and Duncan, G. W.: Anaphylactoid Purpura Simulating Acute Regional Ileitis, Brit. J. Surg. **29**:253, 1941.

356. Quirno Lavalle, R., and Mallo Huergo, E.: Sindrome abdomenal agudo en el curso del purpura, Prensa méd. argent. **29**:590, 1942.

357. Looper, E. A.: Bronchial Involvement in Purpura Hemorrhagica, Ann. Otol., Rhin. & Laryng. **51**:1106, 1942.

The clinical characteristics of Werlhof's disease were present in a patient seen by Reimann.[358] An uncontrollable and fatal hemorrhagic diathesis ensued, despite the fact that the bleeding and clotting times, the number of platelets, the fibrinogen content of the plasma and the level of vitamin C in the blood were normal. A thrombolytic principle was demonstrated in the patient's plasma which when added to normal blood caused dissolution of the clot. It was suggested that this thrombolytic activity was responsible for the hemorrhagic diathesis.

Lucia and Aggeler[359] discuss the history of bruising following slight trauma in patients who do not have spontaneous purpura. "Single easy bruisability," as the authors designate the condition, occurs predominantly in women. The skin of the patients is usually fair, thin and unduly sensitive to light. No symptoms of a hemorrhagic disorder are present except for infrequent attacks of epistaxis and gingival bleeding after brushing the teeth, but excessive bleeding may occur following tonsillectomy or extraction of a tooth. Twenty-three patients were studied to detect any abnormalities indicative of a tendency toward bleeding, and the most significant finding was a slight prolongation of the bleeding time in six cases. The authors feel that simple, easy bruisability was due not to a defect in the blood but to thinness of the skin and defective cushioning of the subcutaneous vascular bed. The symptom may disappear spontaneously but is occasionally present from childhood as a lifelong affliction.

Hemophilia.—Lyophilized plasma is as effective as citrated blood in reducing the coagulation time in hemophilia, according to Johnson.[360] The successful management of hemarthrosis, hematuria and hemorrhage following extraction of teeth with lyophilized plasma is reported. The administration of this prepared plasma likewise proved effective in prophylaxis against recurrent hemorrhage. The coagulation time is lowered rapidly, as with citrated blood; the maximum decrease occurs within fifteen minutes. To prevent loss of thromboplastic activity, the plasma should be frozen and dried within a few hours after its removal from the donor. The lyophilized material may be stored at 5 C. for at least three months without deterioration. Transfusions of 125 to 150 cc. of reconstituted plasma exerted maximum therapeutic benefit, and larger amounts did not produce any further decrease in coagulation time.

The clot resistance was found by Copley and Lalich[361] to be decreased in 2 patients with hemophilia. The clot resistance was determined by a method of the authors described elsewhere (page 205). No direct relation was observed between the coagulation time and the clot resistance. The subcutaneous injection of extracts of bursa pastoris (shepherd's purse) combined with transfusions of blood increased the clot resistance. The hemostatic action of bursa pastoris may depend on several principles, as it contains oxalic acid, dicarboxylic acid and phytothrombin.

Norcross[362] studied a patient with hemophilia associated with vitamin C deficiency. The decreased capillary resistance to negative pressure was corrected

358. Reimann, F.: Purpura Thrombolytica: Ein Beitrag zur Pathogenese der hämorrhagischen Diathese, Acta med. Scandinav. **107**:95, 1941.

359. Lucia, S. P., and Aggeler, P. M.: Simple Easy Bruisability: A Pseudohemorrhagic Diathesis of Probable Endocrine Origin, J. Clin. Endocrinol. **2**:457, 1942.

360. Johnson, J. B.: Management of Hemophilia, with Lyophile Human Plasma Intravenously Injected, J. A. M. A. **118**:799 (March 7) 1942.

361. Copley, A. L., and Lalich, J. J.: The Influence of Blood Transfusion and Injections of Bursa Pastoris (Shepherd's Purse) Extract on the Clot Resistance in Two Hemophiliacs, Am. J. M. Sc. **204**:665, 1942.

362. Norcross, J. W.: Hemophilia and Avitaminosis C.: Report of a Case, Lahey Clin. Bull. **2**:219, 1942.

by administration of ascorbic acid and orange juice, with cessation of recurrent attacks of hemarthrosis. The coagulation time was not influenced by the vitamin C therapy, and it was suggested that the clinical improvement was related to increased capillary resistance.

The treatment of 32 patients for hemophilia with an extract of plant origin is reported by Hecht.[363] The exact source and chemical nature of this extract, called haemostypticum-Hecht, are not stated. It is said to be protein free and was nontoxic to animals into which it was injected. The clot formed in vitro after addition of the extract to hemophilic blood is similar to that of normal blood. In 12 patients in whom bleeding had been continuous for two to eight days, all hemorrhage ceased within ten minutes after intravenous administration of this agent. Used prophylactically before dental extraction and operative procedures in the nose and the throat, the substance prevented abnormal bleeding. Continuous therapy over a three year period was given to 2 patients with hemophilia, and they remained free from hemorrhage.

Hemophilia is a deficiency disease, according to Van Creveld,[364] who reports his experimental studies in support of this hypothesis. He feels that the absence of a plasma factor is responsible for the coagulation defect. A coagulation-promoting substance isolated from normal plasma by Van Creveld exerted a strong coagulating effect on hemophilic blood both in vitro and in vivo. This substance appears to be associated with the euglobulin fraction of plasma protein. It is practically absent from the plasma of a person with hemophilia but is found in the plasma of the parents of one afflicted with this disease. Van Creveld includes in the group of cases of sporadic hemophilia the isolated cases in which an extensive family history fails to reveal the disease in any of the patient's antecedents. To explain the occurrence of the disease in such circumstances one must assume either a mutation to the hemophilic trait or a latent inherited inclination to the disease carried through several generations without clinical manifestations. Three cases of sporadic hemophilia are presented, all with a prolonged coagulation time and with absence of the coagulation-promoting substance from the plasma.

A 43 year old man with a familial and a clinical history of hemophilia was studied by Lawrence and Johnson.[365] A circulating anticoagulant was demonstrated in his blood, and the coagulation time was only slightly decreased following a transfusion of blood. This patient's blood was transfused into a person known to have hemophilia, with subsequent prolongation of the coagulation time of the blood of the recipient. The authors feel that their patient had true hemophilia and that, in addition, his blood exhibited a circulating anticoagulant. The anticoagulant was neither heparin nor antithrombin. They suggest that further investigation be made with reference to the presence of a circulating anticoagulant in the blood of patients with hemophilia when the coagulation time is not appreciably shortened following transfusion of normal blood.

Tocantins [366] collected under special precautions the plasma of hemophiliacs and of normal persons. Following incubation, the plasma specimens were added to aqueous extracts of brain tissue. The hemophilic plasma decreased the thromboplastic activity of the tissue extracts far more than did the normal plasma. This

363. Hecht, E.: Haemophilie: Eine neue Therapie, Acta med. Scandinav. **109**:177, 1941.

364. van Creveld, S.: Sporadic Hemophilia and Pseudo-Hemophilia, Acta pædiat. **29**:37, 1941.

365. Lawrence, J. S., and Johnson, J. B.: Presence of Circulating Anti-Coagulant in Male Member of Hemophiliac Family, Tr. Am. Clin. & Climatol. A. (1941) **57**:223, 1942.

366. Tocantins, L. M.: Antithromboplastin in Hemophilia: Effect of Intravenous Injection of Hemophiliac's Own Thromboplastinized Plasma, J. Clin. Investigation **21**:646, 1942.

antithromboplastic activity of hemophilic plasma is suggested as the explanation of the delayed coagulation in hemophilic blood and the low thromboplastic content of citrated hemophilic plasma.

Spontaneous hemothorax in a case of hemophilia is reported with roentgen studies by Pendergrass and Neuhauser.[367] The authors state that although most forms of serosal hemorrhage are not infrequent in hemophilia, spontaneous hemothorax is generally unknown.

An extensive review of therapy is given with ninety-seven references by Hecht.[368] The diagnosis, the treatment and the theories as to the genesis of hemophilia are outlined by Hubbard.[369]

The inheritance of a hemophilia-like condition in Poland China swine has been studied by Muhrer, Hogan and Bogart.[370] They found that the characteristics of the bleeding abnormality in the swine closely fulfil the criteria set for the diagnosis of hemophilia. The blood of the swine showed a prolonged coagulation time, a normal bleeding time and normal clot retraction. The coagulation time of the recalcified plasma after either slow or rapid centrifugation was similar to that of hemophilic plasma. The "bleeder" pigs had hemorrhages from minor abrasions, which frequently proved fatal. Hemarthrosis was occasionally observed, according to Bogart and Muhrer.[371] The trait is a simple recessive one and not sex linked. Mertz [372] found the capillary resistance to negative pressure in the affected animals to range from 5 to 35 cm. of mercury, with an average of 19 cm. Animals in which the disease was absent gave values for capillary resistance of 35 to 60 cm. of mercury, with an average of 51 cm. Bleeding time as determined by the Duke method was consistently normal, but the saline bleeding time was found to be six times the normal value.[373]

Copley and Lalich [374] produced a hemophilia-like condition in heparinized mice. A prolonged coagulation time and a bleeding tendency were observed. Irregular shape and retraction of clot and thixotropy, the property of becoming fluid when shaken and then again becoming solid, exhibited by certain gels, were observed.

A proteolytic enzyme was obtained by Tagnon, Davidson and Taylor [375] from normal human plasma, with the property of lysing both fibrin and fibrinogen. This enzyme, obtained by treating platelet-free, calcium ion–free plasma with chloroform, can change prothrombin to thrombin without the presence of calcium. No prothrombin or fibrinogen was present in the enzymatic preparation, and the enzyme was found to be associated with the globulin fraction of the chloroform-

367. Pendergrass, E. P., and Neuhauser, E. B. D.: Pleural Lesions in Hemophilia: Report of a Case, Am. J. Roentgenol. **48**:147, 1942.

368. Hecht, E.: Hæmophilie: Kritik der Therapie, Acta med. Scandinav. **109**:155, 1941.

369. Hubbard, W. E.: Hemophilia, Nat. Eclectic M. A. Quart. **33**:26, 1942.

370. Muhrer, M. E.; Hogan, A. G., and Bogart, R.: Defect in Coagulation Mechanism of Swine Blood, Am. J. Physiol. **136**:355, 1942.

371. Bogart, R., and Muhrer, M. E.: Inheritance of a Hemophilia-Like Condition in Swine, J. Hered. **33**:59, 1942.

372. Mertz, E. T.: Anomaly of Normal Duke's and Very Prolonged Saline Bleeding Time in Swine Suffering from Inherited Bleeding Disease, Am. J. Physiol. **136**:360, 1942.

373. Mertz, E. T.: Abnormal Capillary Resistance in Swine Suffering from an Inherited Bleeding Disease, Am. J. Physiol. **138**:136, 1942.

374. Copley, A. L., and Lalich, J. J.: Experimental Production of Hemophilia-Like Condition in Heparinized Mice, Am. J. Physiol. **135**:547, 1942.

375. Tagnon, H. J.; Davidson, C. S., and Taylor, F. H. L.: Studies on Blood Coagulation: A Proteolytic Enzyme Prepared from Calcium and Platelet Free Normal Human Blood Plasma, J. Clin. Investigation **21**:525, 1942.

containing plasma. When hemophilic plasma is treated similarly with chloroform, the enzyme obtained differs from that of normal plasma.[376] This indicates, according to the authors, that in hemophilia the deficiency of a factor associated with the globulin fraction of plasma is paralleled by a deficiency of the proteolytic activity of the globulin fraction of chloroform plasma.

Telangiectasia.—Hereditary telangiectasis, according to Stellar,[377] has been reported in the literature in 550 members of 90 to 95 families to the end of 1930. He adds the case of a woman of 56 years in which recurrent epistaxis preceding the menses was present from puberty. In later life gastrointestinal hemorrhage developed in this patient, and hemoglobin values below 10 per cent were recorded on four separate admissions to the hospital.

Congenital afibrinogenemia was studied by Van Creveld [364] in the younger of twins. By the method of analysis employed, no trace of fibrinogen could be demonstrated in the plasma. A bleeding tendency and a prolonged coagulation time were manifest at the sixth week of age. The elder twin was normal. Necropsy revealed extensive hemorrhages into all body cavities. The author also draws attention to the rare instance of the presence at an early age of a prolonged coagulation time, associated with a bleeding tendency that in later life disappeared with return of the coagulation time to normal.

Blood Platelets.—In 23 cases, after various operations, Shapiro, Sherwin and Gordimer [378] determined daily the number of platelets per cubic millimeter of blood, the coagulation time and the prothrombin time. No change in the coagulation time was observed by the Lee and White method, but between the fifth and the fourteenth postoperative day an increase in the platelets occurred, attaining levels one and one-half to two times the previous values, with simultaneous lessening of the difference between the prothrombin times of undiluted and 25 per cent diluted plasma. This change, which was observed in 14 of the cases, was evidently due to shortening of the prothrombin time of the diluted plasma. In 3 cases the difference decreased to less than three seconds, with development of pulmonary infarction in 2 and thrombophlebitis in all. These studies indicate that both the prothrombin and the thromboplastin of the blood increase in concentration or in activity in the postoperative period at the time when the incidence of postoperative thromboembolization is greatest.

Wright [379] studied the stickiness of blood platelets following surgical operation and childbirth. Serial observations of the platelet count and the stickiness revealed an increase in both beginning on the fourth postoperative or postpartum day and reaching a maximum on the tenth day. The increased tendency of the platelets to adhere to surfaces was attributed to the appearance of young forms in the circulation. Both the thrombocytosis and the greater adhesiveness of the platelets were suggested as contributing factors in the postoperative formation of thrombi.

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376. Tagnon, H. J.; Davidson, C. S., and Taylor, F. H. L.: Relationship of the Coagulation Defect in Hemophilia to a Plasma Proteolytic Enzyme, J. Clin. Investigation **21**:632, 1942.

377. Stellar, L. I.: Hereditary Telangiectasis: Report of a Case, New England J. Med. **226**:336, 1942.

378. Shapiro, S.; Sherwin, B., and Gordimer, H.: Postoperative Thromboembolization: Platelet Count and Prothrombin Time After Surgical Operations; Simple Method for Detecting Reductions and Elevations of Prothrombin Concentration (or Activity) of Blood Plasma, Ann. Surg. **116**:175, 1942.

379. Wright, H. P.: Changes in the Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, J. Path. & Bact. **54**:461, 1942.

The addition of heparin to dogs' blood in vitro resulted in a decrease in the platelet count, according to Copley and Robb.[380] Following intravenous administration of heparin to dogs,[381] an initial drop in platelets was followed by a rise. Lindelöf [382] gave sulfapyridine to rabbits and observed no significant changes in the platelet counts, but after administration of sulfathiazole mild thrombopenia developed in these animals. Sonder [383] studied by means of the dark field the action of various anticoagulants on blood platelets and found that a 1 per cent solution of sodium oxalate exerted a damaging effect on them, whereas in a 2 per cent solution of sodium citrate the platelets remained in a quiescent state with little evident ameboid motion. A solution designated as liquemin allowed observation of the dissolution of platelets and the formation of fibrin reticulum. Catel and Schotola [384] found that some samples of sesame oil when orally administered to normal persons raised the platelet count.

An indirect method of enumerating blood platelets on dried blood films, stained with brilliant cresyl while wet, is described by Pernokis.[385a] This is not a new method; it is described in the "Manual of Clinical and Laboratory Technic" by Weiss and Isaacs.[385b] Copley and Robb [386] demonstrated that the direct method of Vilariño and Pimentel for counting thrombocytes is accurate and has the advantage that the count need not be performed immediately. It depends on separation of the platelets and the erythrocytes by centrifugation and preservation of the forms in a diluting fluid containing formaldehyde. A simplifying modification of the original technic is offered.

Capillary Fragility.—The role of capillary integrity as a factor in the hemorrhagic diathesis receives increasing attention. Scarborough [387] believes that a substance (or substances) present in fruit, aside from ascorbic acid, is capable of increasing the resistance of capillary walls to negative pressure. The therapeutic efficacy of this substance, designated vitamin P, has not, as yet, been demonstrated. Higby [388] reviewed the literature dealing with the chemical nature of hesperidin and its experimental use as a source of vitamin P. Lindheimer, Hinman and Halliday [389] discussed clinical investigations with vitamin P. Cameron and Mills [390] administered this vitamin in a case of scurvy and found that the hemorrhagic manifestations of the disease were corrected promptly, but until vitamin C was added, the other aspects of the disease remained unchanged.

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380. Copley, A. L., and Robb, T. P.: Studies on Platelets: The Effect of Heparin on the Platelet Count in Vitro, Am. J. Clin. Path. **12**:416, 1942.

381. Copley, A. L., and Robb, T. P.: Studies on Platelets: Effect of Heparin in Vivo on Platelet Count in Mice and Dogs, Am. J. Clin. Path. **12**:563, 1942.

382. Lindelöf, S. A. J.: Ueber den Einfluss einiger Sulfonamidpräparate auf den Gehalt des Blutes an Thrombozyten und weissen Blutkörperchen bein Kaninchen, Upsala läkaref. förh. **47**:171, 1942.

383. Sonder, S.: Der Einfluss verschiedener gerinnungshemmender Lösungen auf die Evolutionsformen der Thrombozyten, Helvet. med. acta **8**:436, 1941.

384. Catel, W., and Schotola, H.: Ueber den Einfluss des A-Vitamins und des Sesamöls auf die Zahl der Blutplättchen, Klin. Wchnschr. **20**:1119, 1941.

385. (*a*) Pernokis, E. W.: Simple Method of Evaluating Blood Platelets, J. Lab. & Clin. Med. **27**:1069, 1942. (*b*) Weiss, H. B., and Isaacs, R.: Manual of Clinical and Laboratory Technic, Philadelphia, W. B. Saunders Company, 1940.

386. Copley, A. L., and Robb, T. P.: Studies on Platelets: The Method of Vilariño and Pimentel and a New Direct Method of Counting Blood Platelets, Am. J. Clin. Path. **12**:362, 1942.

387. Scarborough, H.: Vitamin P, Biochem, J. **33**:1400, 1939; Scarborough,[325] p. 408.

388. Higby, R. H.: The Chemical Nature of Hesperidin and Its Experimental Medical Use as a Source of Vitamin P: A Review, J. Am. Pharm. A. (Scient. Ed.) **30**:629, 1941.

389. Lindheimer, G. T.; Hinman, W. F., and Halliday, E. G.: The Function and Occurrence of Citrin ("Vitamin P"), J. Am. Dietet. A. **18**:503, 1942.

390. Cameron, D. G., and Mills, E. S.: Scurvy in Montreal, Canad. M. A. J. **46**:548, 1942.

Vitamin C administered as crystalline ascorbic acid did not alter capillary resistance as measured by negative pressure methods in normal subjects, according to Levcowich and Batchelder.[391] Scarborough [387] states that he has never been able to increase capillary resistance with vitamin C except in special circumstances. He feels that the measurement of capillary resistance for the detection of subclinical scurvy is unjustified. Munro, Lazarus and Bell [392] determined capillary fragility for 182 medical students in England and compared the results with those for a group studied before the war. No significant difference was noted. Pignoli [393] found that the capillary resistance of normal women remained unaltered during the greater part of the menstrual cycle but that a slight decrease occurred in the last days of the old and the first days of the new cycle.

No change in vascular fragility as tested by negative pressure was observed by Schaefer [394] in patients with leukemia, anemia and polycythemia, but increased fragility was associated with infectious and inflammatory diseases and disorders of the vascular system.

Bell and his collaborators [395] compared the results obtained for 142 medical students by the negative suction method of Dalldorf and Russell with those obtained by the positive pressure test of Göthlin and found a low degree of correlation between them. From the results of one method it was impossible to predict the readings by the other procedure, nor was a conclusion reached as to which method of measuring capillary fragility was preferable. Each test proved consistent with itself.

Menkin [396] demonstrated that extracts of adrenal cortex and certain derived steroid fractions when administered to rabbits inhibited the increased permeability associated with inflammatory exudates. Observations made on capillary permeability in rabbits after injections of histamine were reported by Rigdon,[397] and observations on capillary permeability and inflammation in the skin of sensitized rabbits, by Rigdon and Haynes.[398] Zon, Ceder and Crigler [399] reported that administration of antiplatelet serum to rabbits prevents the normal increase of histamine in inflammatory lesions of the skin. Levy and Appleton [400] isolated from saliva a substance in crystalline form which increased capillary permeability. It is biologically similar to leukotaxine.

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391. Levcowich, T., and Batchelder, E. L.: Ascorbic Acid Excretion at Known Levels of Intake as Related to Capillary Resistance, Dietary Estimates, and Human Requirements, J. Nutrition **23**:399, 1942.

392. Munro, H. N.; Lazarus, S., and Bell, G. H.: Capillary Fragility in Peace and War: Statistical Comparison, Lancet **1**:648, 1942.

393. Pignoli, R.: Capillary Fragility in the Meno-Metrorrhagies and Its Changes Following Treatment with Ascorbic Acid, Ginecologia **7**:85, 1941.

394. Schaefer, W.: Untersuchungen über die Gefässzerreisslichkeit bei internen Erkrankungen, Ztschr. f. d. ges. exper. Med. **108**:725, 1941.

395. Bell, G. H.; Munro, H. N.; Lazarus, S., and Scarborough, H.: Capillary Fragility (Resistance); Negative- and Positive-Pressure Test Compared, Lancet **2**:536, 1942.

396. Menkin, V.: Further Studies on Effect of Adrenal Cortex Extract and of Various Steroids on Capillary Permeability, Proc. Soc. Exper. Biol. & Med. **51**:39, 1942.

397. Rigdon, R. H.: Observations on Effect of Histamine Phosphate on Capillary Permeability and Inflammation, J. Lab. & Clin. Med. **27**:1554, 1942.

398. Rigdon, R. H., and Haynes, A.: Observations on Capillary Permeability and Inflammation in the Skin of Sensitized Rabbits, J. Lab. & Clin. Med. **27**:598, 1942.

399. Zon, L.; Ceder, E. T., and Crigler, C.: Presence of Histamine in Inflammatory Lesions, Arch. Path. **33**:452 (April) 1942.

400. Levy, B. M., and Appleton, J. L. T.: Effects of Saliva on Capillary Permeability, J. Dent. Research **21**:505, 1942.

Hemostasis and Coagulants.—The mechanism of the coagulation of blood and of hemostasis is reviewed by Moore [401] and Hansen.[402] Lozner, Taylor and Taylor [403] investigated the so-called coagulation defect in menstrual blood and showed that the fluidity results from absence of both prothrombin and fibrinogen and that in effect the menstrual fluid is blood that has already undergone formation of clot and is therefore a suspension of formed blood elements and tissue debris in serum. It behaves similarly to defibrinated blood when added to solutions of thrombin, prothrombin and fibrinogen.

The lesions occurring in multiple sclerosis have been attributed tentatively to thrombosis of veins in the brain and the spinal cord. Exacerbation of the symptoms has been found to follow factors which some observers believe predispose to disturbance in the blood plasma secondary to thrombosis. Simon [404] studied the decrease in the blood coagulation time after the intravenous administration of typhoid vaccine and epinephrine in patients with disseminated sclerosis and patients with other diseases of the brain stem and spinal cord. After the injection of typhoid vaccine the clotting time of blood was reduced 25 per cent or more, and this change lasted three times longer in patients with multiple sclerosis. One patient was given a second dose of typhoid vaccine two weeks after the initial injection. The response of the clotting time was so much more intense and prolonged than initially that further studies were not attempted. The author suggests that in patients with multiple sclerosis there is a constitutional or an acquired sensitivity to stimuli which tends to reduce the blood coagulation time. Intensive or repeated stimulation of this hypersensitive mechanism under certain circumstances may lead to intravascular thrombosis.

The pharmacodynamics and the metabolism of oxalic acid are reviewed by Blain and Campbell.[405] A greater part of the one hundred and seventy-five articles published within the past decade appeared in foreign language journals. The intravenous administration of oxalic acid to rabbits was found to reduce the blood coagulation time by 44 per cent in fifteen minutes and by 54 per cent in one hour. Oxalic acid was given intravenously to 440 patients who had undergone a great variety of major operative procedures and produced either an immediate cessation of hemorrhage or a noticeable decrease in oozing in practically all cases. This material appeared to be most efficacious in controlling hemorrhage from large oozing surfaces. Between 20 and 40 mg. administered intravenously proved to exert the optimal effect, and, if indicated, this amount could be given again in a short time. As a hemostatic agent oxalic acid proved safe, reliable, inexpensive and almost instantly effective. The use of oxalic acid in the treatment of hemophilia is reviewed in connection with that disease.

Tagnon and Taylor [406] administered a pseudoglobulin obtained from rabbit plasma orally to dogs, normal human subjects and to 2 patients with hemophilia.

401. Moore, C. V.: Blood Coagulation and Hemostasis, West. J. Surg. **50**:402, 1942.

402. Hansen, H. L.: Blood Coagulation and Hemostatic Agents, J. Am. Dent. A. **29**:673, 1942.

403. Lozner, E. L.; Taylor, Z. E., and Taylor, F. H. L.: The So-Called "Coagulation Defect" in Menstrual Blood, New England J. Med. **226**:481, 1942.

404. Simon, B.: Blood Coagulation in Disseminated Sclerosis and Other Diseases of Brain Stem and Cord, Arch. Neurol. & Psychiat. **48**:509 (Oct.) 1942.

405. Blain, A. W., and Campbell, K. N.: Hemostatic Effect of Oxalic Acid: Clinical and Experimental Results, with Review of Literature, Arch. Surg. **44**:1117 (June) 1942.

406. Tagnon, H. J., and Taylor, F. H. L.: Effect on Coagulation Time of Oral Administration of Rabbit Thrombin, Proc. Soc. Exper. Biol. & Med. **49**:32, 1942.

A prompt fall in the coagulation time occurred in each instance. A gradual return to the preinjection level began two hours later.

Cunningham [407] noted that the application of sulfapyridine to experimental wounds exerted a hemostatic effect. Secondary and delayed tonsillar hemorrhages were controlled clinically by the application of sulfapyridine powder to the oozing surface. Sulfanilamide and sulfathiazole proved of little hemostatic value. Rutturk [408] found that hemostyphin, a lipoid of unknown constitution prepared from animal phosphatides, reduced the bleeding time in rabbits when applied locally to cutaneous wounds. The hemostatic property of human milk was investigated by Hecht,[409] together with the role of ascorbic acid, in the physiology of coagulation. The influence on coagulation of dog plasma exerted by mother's milk was found to be independent of its content of vitamin C or of lipoid phosphorus. The hemostatic property of milk was less active during the colostrum period than in the later stages of lactation. Extracts of the parotid gland of the toad Bufo bufo, used by Derouaux,[410] failed to exert any hemostatic action on the bleeding time of rabbits.

The clotting time of plasma in glass, paraffin, collodion, and lusteroid containers was investigated by Lozner, Taylor and MacDonald.[411] In a glass tube the plasma clotted in eleven minutes; in the other tubes, in from four to six times as long. Similar results were obtained with platelet-rich and with platelet-free plasma. If the plasma was first incubated in glass tubes and then added to hemophilic blood, the clot-promoting activity was two and a half times that of plasma incubated in the other three types of containers. The authors suggest that the "physiologic anticoagulant" responsible for the fluidity of circulating blood may be an attribute of the vascular endothelium which resembles physically such surfaces as collodion, paraffin and lusteroid. The experimental results indicate that a foreign surface acts by modifying some constitutent of cell-free plasma. Platelet counts remained unchanged in citrated plasma exposed for one hour to the surface materials under study.

Schutz [412] reports studies of the influence of electric currents and electrically charged surfaces on blood coagulation. The clotting of fresh whole blood was observed to be delayed by weak direct currents and, depending on the metal used as the electrode, a variable effect was noted on the coagulation of the blood in contact with the electrodes.

Ferguson [413] studied an exceptionally stable prothrombin-free fibrinogen. On the basis of his observations, he feels that the formation of fibrin under the specific influence of thrombin is not related to denaturative and digestive phenomena. He offers a criticism of the theory of blood clotting incorporating such views.

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407. Cunningham, B. P.: Clinical and Experimental Studies with Sulfapyridine as Hemostatic Agent, Ann. Otol., Rhin. & Laryng. **51**:301, 1942.

408. Rutturk, J.: On Haemostyptics: Hemostyphin and Manetol, Arch. internat. de pharmacodyn. et de thérap. **67**:305, 1942.

409. Hecht, E.: Zur Kenntnis der Blutgerinnung: Vitamin C in der Blutgerinnungsphysiologie, Acta med. Scandinav. **109**:81, 1941.

410. Derouaux, G.: Action du venin de crapaud sur le temps de saignement, Arch. internat. de pharmacodyn. et de thérap. **66**:325, 1941.

411. Lozner, E. L.; Taylor, F. H. L., and MacDonald, H.: Effect of Foreign Surfaces on Blood Coagulation, J. Clin. Investigation **21**:241, 1942.

412. Schutz, F.: On the Influence of Weak Electric Currents and Electrically Charged Surfaces on Blood Coagulation, J. Physiol. **101**:27, 1942.

413. Ferguson, J. H.: Flocculation Maximum (p_H) of Fibrinogen and Some Other Blood-Clotting Reagents (Relative Turbidimetry with Evelyn Photoelectric Colorimeter), J. Gen. Physiol. **25**:607, 1942.

From normal dog plasma Tagnon [414] obtained an enzyme which possessed characteristics resembling those of trypsin. It lysed fibrinogen except in the presence of prothrombin; in the presence of the latter, coagulation intervened, followed by fibrinolysis. As the enzyme reacts with prothrombin to form thrombin without the intervention of calcium or thromboplastin, it was suggested that it plays a primary role in the normal coagulation of blood. Kaplan, Tagnon and collaborators [415] obtained from steer, swine and human plasma an enzyme capable of digesting fibrinogen, fibrin, gelatin and casein. This enzyme was absent in horse plasma.

A method for the quantitative measurement of the retraction of blood clots is offered by Aggeler, Lucia and Hamlin,[416] based on an estimation of the extracorpuscular volume of the clot. After normal coagulation of the blood has occurred, the specimen is incubated for one hour at 37 C. The clot volume is obtained by subtracting the residual serum volume, after removal of the clot, from the total volume of the specimen. The difference between the percentage of the packed cell volume, obtained by centrifugation of a separate oxalated blood sample, and the percentage of the clot volume, is a measure of the extracorpuscular volume of the clot. An average value of 9.1 per cent was obtained for 100 normal subjects, with a range of minus 5.9 to plus 24.1 per cent. The significance to be attached to variations in the extracorpuscular volume of the clot is discussed by Lucia, Aggeler and Hamlin.[417] Diminished clot retraction was seen in hypoprothrombinemia and thrombopenia. However, similar results might occur when neither of these conditions is present, as in "thrombasthenia," fibrinogenopenia or "fibrinasthenia" or in the presence of a circulating inhibitor of clot retraction.

Hirschboeck and Coffey [418] measured the clot retraction time as the interval between the complete formation of the clot and the beginning of its separation from the sides of a glass container. This procedure was used [419] in 10 cases of pulmonary embolism, and retraction was found to begin in less than ten minutes in 9 instances. In the case of a normal person retraction begins in twenty-five to thirty minutes. The authors considered all postoperative patients with a clot retraction time of less than ten minutes as possible candidates for pulmonary embolism and suggested the use of this test as a guide to the selection of patients for prophylactic heparinization.

The tensile strength and the stretch of plasma clots were studied by Tarlov, Goldfarb and Benjamin.[420] The tensile strength of the plasma clots of persons who were ill was found to be greater than that of the plasma clots of normal persons. Lalich and Copley [421] use viscometer tubes in the determination of clot

414. Tagnon, H. J.: The Significance of Fibrinalysis in the Mechanism of Coagulation of Blood, J. Lab. & Clin. Med. **27**:1119, 1942.

415. Kaplan, M. H.; Tagnon, H. J.; Davidson, C. S., and Taylor, F. H. L.: Studies on Blood Coagulation: The Nature and Properties of a Proteolytic Enzyme Derived from Plasma, J. Clin. Investigation **21**:533, 1942.

416. Aggeler, P. M.; Lucia, S. P., and Hamlin, L. M.: Blood Clot Retraction: Measurement of the Extracorpuscular Volume of the Clot, J. Lab. & Clin. Med. **28**:89, 1942.

417. Lucia, S. P.; Aggeler, P. M., and Hamlin, L. M.: Blood Clot Retraction: Significance of Extracorpuscular Volume of Clot and Its Clinical Application, Am. J. M. Sc. **204**:507, 1942.

418. Hirschboeck, J. S., and Coffey, W. L., Jr.: Method for Measuring Clot Retraction Time, Arch. Path. **33**:380 (March) 1942.

419. Hirschboeck, J. S., and Coffey, W. L., Jr.: Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, J. A. M. A. **118**:1161 (March 28) 1942.

420. Tarlov, I. M.; Goldfarb, A. I., and Benjamin, B.: Method for Measuring Tensile Strength and Stretch of Plasma Clots, J. Lab. & Clin. Med. **27**:1333, 1942.

421. Lalich, J. J., and Copley, A. L.: Study of Clot Firmness in Viscometer Tubes, Proc. Soc. Exper. Biol. & Med. **51**:235, 1942.

firmness. Kershbaum and Schwartz [422] found that blood clots were nonpermeable to sulfonamide compounds in vitro and that neither heparin nor increased temperature induced permeability to such compounds. Bleeding time, lymph time and clot resistance were compared by Copley and Lalich.[423] After a clot had formed in a wound made by puncturing the skin with a mechanical lancet, a positive pressure of 100 mm. of mercury was applied for three minutes to the limb above the site of the wound by means of a blood pressure cuff. Renewed bleeding was not observed in normal persons. In persons with hemophilia the application of the cuff renewed bleeding for as long as seventy-five minutes after the flow of blood had ceased. The author believes that the degree of stiffness of the clot and the ability of the clot to adhere to the skin are a measure of hemostasis.

Dicoumarin.—The synthetic hemorrhagic agent 3, 3′-methylene-bis-(4-hydroxycoumarin), first isolated from spoiled sweet clover, has received extensive clinical trial during the past year. A review of the historical and experimental development of this compound is given by several authors.[424] Allen, Barker and Waugh [424b] used dicoumarin in 374 instances and found it a valuable agent in preventing intravascular thrombosis. The effect of dicoumarin seems to be on prothrombin only. The prolongation of prothrombin time indicates destruction of prothrombin, suppression of its action or inhibition of its formation. Dicoumarin, in addition to prolonging the prothrombin time, impairs clot retraction and accelerates the sedimentation of erythrocytes. After its administration, from twenty-four to forty-eight hours elapse before an effect on the prothrombin time is noted. On discontinuance of the administration of the material, the prothrombin time may be prolonged for two days to three weeks, depending on the amount given. The authors employed a dose of 300 mg. of dicoumarin, given orally, on the first day and 200 mg. on the second day. Thereafter, the 200 mg. dose was repeated each day that the prothrombin time was less than thirty-five seconds as determined by Magath's modification of the Quick method. The importance of daily determinations of prothrombin as a guide to dosage and as a check on variations in effect on individual patients is stressed. Transfusions of fresh blood will temporarily reduce the prothrombin time. Vitamin K is ineffective.

In 69 cases of postoperative pulmonary embolism in which dicoumarin therapy was instituted, subsequent thrombosis or embolism developed in only 2. In neither of these instances was the prothrombin time sufficiently elevated to establish the adequacy of dicoumarin therapy. Untoward bleeding, classed as slight in 17, moderate in 9 and severe in 5, was encountered in 31 instances. Bleeding occurred most commonly from the operative site and was noted in 24 cases. Ecchymosis of the skin, hematuria, epistaxis and cerebral hemorrhage were also encountered. Two patients with subacute bacterial endocarditis who were receiving dicoumarin died. One showed signs of cerebral hemorrhage before death, and the other, extensive hemorrhages in many organs and tissues at necropsy. A tendency to bleed into the kidney or into the brain in bacterial endocarditis

422. Kershbaum, A., and Schwartz, L.: Non-Permeability of Blood Clot to Sulfonamide Drugs in Presence of Increased Temperature, Proc. Soc. Exper. Biol. & Med. **50**:165, 1942.

423. Copley, A. L., and Lalich, J. J.: Bleeding Time, Lymph Time, and Clot Resistance in Man, J. Clin. Investigation **21**:145, 1942.

424. (*a*) Wright, I., and Prandoni, A.: The Dicoumarin 3,3′-Methylene-Bis (4-Hydroxycoumarin): Its Pharmacologic and Therapeutic Action in Man, J. A. M. A. **120**:1015 (Nov. 28) 1942. (*b*) Allen, E. V.; Barker, N. W., and Waugh, J. M.: A Preparation from Spoiled Sweet Clover (3,3′-Methylene-Bis [4-Hydroxycoumarin]) Which Prolongs Coagulation and Prothrombin Time of the Blood: A Clinical Study, ibid. **120**:1009 (Nov. 28) 1942. (*c*) Meyer, O. O.; Bingham, J. B., and Axelrod, V. H.: Studies on the Hemorrhagic Agent, 3,3′-Methylene-Bis (4-Hydroxycoumarin): The Method of Administration and Dosage, Am. J. M. Sc. **204**:11, 1942.

is present without the administration of dicoumarin, and the authors feel that this agent is contraindicated in this disease.

Meyer, Bingham and Axelrod [424c] administered dicoumarin to 73 patients, and except for a gross hemorrhage developing at the site of uterine curettage in 1, no toxic or untoward effects were noted. Studies of hepatic and of renal function were made in many instances while complete blood counts, a urinalysis, determinations of blood sugar and nonprotein nitrogen and Rumpel-Leede tourniquet tests were done in all cases. In no case was there observed a significant quantitative change in any test following the administration of dicoumarin. Prothrombin time and coagulation time were determined daily. The disodium salt of dicoumarin, was given intravenously, 4 Gm. per kilogram of body weight, to 27 patients, and this treatment was repeated when indicated. A latent period of two to five days elapsed before the treatment attained maximal effectiveness, and no significant advantage of intravenous over oral administration was noted. An oral dose of 5 mg. of dicoumarin per kilogram of body weight, followed by a daily dose of 1.5 mg. per kilogram was given in 46 cases. It is imperative to measure the prothrombin and coagulation times daily to control individual variation in response.

Butsch and Stewart [425] warn that dicoumarin should be used with caution or not at all in cases in which an ulcerating or granulating lesion is present. They noted hematemesis following its administration in 2 of 4 cases of carcinoma of the stomach; 1 case terminated fatally. Debilitated and cachetic patients proved more susceptible to the effects of the drug.

Single oral doses of dicoumarin were given by Stats and Bullowa [426] to 39 hospitalized persons. In 2 minor epistaxis developed, and 4 others came to necropsy. One showed unusual edema and intense hyperemia of the bronchi and a large quantity of hemorrhagic fluid within the bronchi. No lesions referable to dicoumarin were seen in the other 3 patients.

Vitamin K is reported by most authors as being ineffective in correcting the prothrombin time after administration of dicoumarin. Townsend and Mills [427] gave vitamin K to a patient while dicoumarin was still being administered and observed no further rise in the prothrombin or the coagulation time.

Dicoumarin synthesized in Sweden was used by Lehmann [428] in the treatment of 17 patients with thrombosis of the veins of the extremities. An oral dose of 0.75 Gm. did not lower the prothrombin content of the blood as effectively as a similar dose administered to normal persons. The author [429] gave dicoumarin to lactating women and observed a lowering of the prothrombin content of the blood of both mothers and nursing infants. A preliminary report of the clinical use of dicoumarin in effectively prolonging the prothrombin and coagulation times is given by Le Fevre.[430]

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425. Butsch, W. L., and Stewart, J. D.: Clinical Experiences with Dicoumarin: 3,3'-Methylene-Bis-(4-Hydroxycoumarin), J. A. M. A. **120**:1025 (Nov. 28) 1942.

426. Stats, D., and Bullowa, J. G. M.: Effect of a Single Dose of 3,3'-Methylene-Bis (4-Hydroxycoumarin) upon Blood Coagulation in Humans, Proc. Soc. Exper. Biol. & Med. **50**:67, 1942.

427. Townsend, S. R., and Mills, E. A.: The Effect of the Synthetic Haemorrhagic Agent, 3,3'-Methylene-Bis (4-Hydroxycoumarin) in Prolonging the Coagulation and the Prothrombin Time in the Human Subject, Canad. M. A. J. **46**:214, 1942.

428. Lehmann, J.: Hypoprothrombinaemia Produced by Methylene-Bis (Hydroxycoumarin): Its Use in Thrombosis, Lancet **1**:318, 1942.

429. Lehmann, J.: Hypoprothrombinemia Produced by 3,3'-Methylene-Bis (4-Hydroxycoumarin) and Its Use in the Treatment of Thrombosis, Science **96**:345, 1942.

430. Le Fevre, F. A.: The Effects of 3,3'-Methylene-Bis (4-Hydroxycoumarin), (Dicoumarol) on the Prothrombin and Coagulation Times of the Blood: Preliminary Report, Cleveland Clin. Quart. **9**:147, 1942.

Prandoni and Wright [431] review and compare the modes of action and the indications for the use of heparin and dicoumarin. Heparin must be given intravenously; it is effective immediately after administration, and the duration of action is from one to four hours. Dicoumarin must be administered by mouth; it is not effective for twenty-four to seventy-two hours after the initial dose, but the average duration of its action is eleven days. A hemorrhagic syndrome was observed by the author in 8 patients who were receiving dicoumarin. In this group no single factor could be found responsible for the hemorrhagic complications. It was thought that individual susceptibility was in part responsible for the variations.

Hobson and Witts [432] state that misleading results are obtained if rabbit brain is used as a source of thromboplastin in the determination of prothrombin time after the administration of dicoumarin. They recommend either emulsions of fresh human brain or Russell viper venom with lecithin.

The employment of lusteroid tubes for the determination of the coagulation time of venous blood is suggested by Davidson and MacDonald.[433] An index of early changes in the coagulation of the circulating blood is obtained by this method which is not seen when glass tubes are employed.

Most laboratory animals dying from lethal doses of dicoumarin show hemorrhages in various organs and pulmonary edema, according to Rose, Harris and Chen.[434] Central necrosis of the liver was found in approximately one half of the rats and occasionally was seen in rabbits, mice and dogs that had died of intoxication with dicoumarin. Richards and Cortell [435] found some evidence of necrosis of the liver in dogs and monkeys after administration of dicoumarin. Guinea pigs on a vitamin C–free diet succumbed to the effects of dicoumarin sooner than animals on a diet rich in vitamin C. Baumann and collaborators [436] found that chlorobutanol and other substances which stimulate the synthesis of vitamin C in rats counteracted in part the hypoprothrombinemia produced by dicoumarin in these animals. The liver is thought to be the common site of origin for both prothrombin and vitamin C in rats, and similar proteins of the liver may be involved in the synthesis of each. However, the nature of these syntheses remains obscure. It is suggested that the activation of prothrombin might involve the action of vitamin C or of vitamin K or of both. Overman, Field, Baumann and Link [437] found that the administration of vitamin K to rats counteracted the hypoprothrombinemia when given before, during or twelve hours after the admin-

431. Prandoni, A., and Wright, I.: The Anticoagulants: Heparin and the Dicoumarin 3,3′-Methylene-Bis (4-Hydroxycoumarin), Bull. New York Acad. Med. **18**:433, 1942.

432. Hobson, F. C. G., and Witts, L. J.: Thromboplastin with Dicoumarin, Brit. M. J. **1**:93, 1942.

433. Davidson, C. S., and MacDonald, H.: An Evaluation of the Use of Dicoumarin, 3,3′-Methylene-Bis (4-Hydroxycoumarin), as an Anticoagulant, and Its Effect on Certain Plasma Constituents, J. Clin. Investigation **21**:644, 1942.

434. Rose, C. J.; Harris, P. M., and Chen, K. K.: Toxicity of 3,3′-Methylene-Bis (4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**:228, 1942.

435. Richards, R. K., and Cortell, R.: Studies on the Anticoagulant 3,3′-Methylene-Bis (4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**:237, 1942.

436. Baumann, C. A.; Field, J. B.; Overman, R. S., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: Induced Vitamin C Excretion in the Rat and Its Effect on the Hypoprothrombinemia Caused by 3,3′-Methylene-Bis (4-Hydroxycoumarin), J. Biol. Chem. **146**:7, 1942.

437. Overman, R. S.; Field, J. B.; Baumann, C. A., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease: Effect of Diet and Vitamin K on Hypoprothrombinemia Induced by 3,3′-Methylene-Bis (4-Hydroxycoumarin) in the Rat. J. Nutrition **23**:589, 1942.

istration of dicoumarin. Using rabbits, Overman, Stahlmann and Link [438] found that the simultaneous oral administration of menadione (2-methyl-1,4-naphthoquinone) and l-ascorbic acid in high doses either drastically reduced or completely nullified the anticoagulant action of dicoumarin. Similar results were obtained with menadione alone, but after the exclusive administration of l-ascorbic acid only 15 of 50 rabbits were protected. In doses sufficient to alleviate vitamin K deficiency menadione did not inhibit the anticoagulant action of dicoumarin. Bollman and Preston [439] showed that in dogs large amounts of sulfathiazole failed to alter the effectiveness of dicoumarin. Preexisting vitamin K deficiency, inanition, hepatic injury or renal injury exaggerated the prolongation of the prothrombin time. McGinty and collaborators [440] gave purified beef prothrombin intravenously to dogs with lowered prothrombin levels as a result of previous administration of dicoumarin and observed a prompt rise in the concentration of plasma prothrombin. The action of the injected prothrombin persisted for two to three days. Studies on the plasma prothrombin time of rats, guinea pigs and dogs following the administration of dicoumarin are reported by Overman and his associates.[441]

Anticoagulants.—Methods for the assay of heparin are given by Seegers [442] and by Foster.[443] Magerl [444] injected bacteria into heparinized rabbits and observed in the subsequent leukocyte response an increased percentage of lymphocytes and a decreased percentage of polymorphonuclear cells. Heparin failed to inhibit the enhancing effect exerted on blood coagulation in vitro by certain strains of staphylococci, according to Rigdon and Haynes.[445]

Sodium hexametaphosphate was shown by Caspe and Hadjopoulos [446] to be an effective anticoagulant for rabbits' blood both in vitro and in vivo.

Prothrombin and Vitamin K.—The clinical aspects of vitamin K therapy are reviewed by Smith and Warner [447] and the development and the chemistry of vitamin K compounds by MacCorquodale.[448] The present concepts of the coagulation of blood with particular reference to the role of vitamin K are covered

438. Overman, R. S.; Stahlmann, M. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: The Effect of 2-Methyl-1,4-Naphthoquinone and L-Ascorbic Acid upon the Action of 3,3'-Methylene-Bis (4-Hydroxycoumarin) on the Prothrombin Time of Rabbits, J. Biol. Chem. **145**:155, 1942.

439. Bollman, J. L., and Preston, F. W.: The Effects of Experimental Administration of Dicoumarin: 3,3'-Methylene-Bis (4-Hydroxycoumarin), J. A. M. A. **120**:1021 (Nov. 28) 1942.

440. McGinty, D. A.; Seegers, W. H.; Pfeiffer, C. C., and Lowe, E. R.: Plasma Prothrombin Concentration in Dogs Given 3,3'-Methylene-Bis (4-Hydroxycoumarin) and Purified Beef Prothrombin, Science **96**:540, 1942.

441. Overman, R. S.; Stahlmann, M. A.; Sullivan, W. R.; Huebner, C. F.; Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: Effect of 3,3'-Methylene-Bis (4-Hydroxycoumarin) on the Prothrombin Time of the Plasma of Various Animals, J. Biol. Chem. **142**:941, 1942.

442. Seegers, W. H.: The Quantity of Thrombin Required to Clot Heparin-Plasma Mixtures, Proc. Soc. Exper. Biol. & Med. **51**:172, 1942.

443. Foster, R. H. K.: The Assay of Heparin, J. Lab. & Clin. Med. **27**:820, 1942.

444. Magerl, J. F.: Ueber den Einfluss von Ultraviolett-Bestrahlungen auf die immunbiologische Wirksamkeit von Eigenblutinjektionen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **99**:378, 1941.

445. Rigdon, R. H., and Haynes, A.: Observations on the Failure of Heparin to Inhibit Clotting of Blood in Vitro by Staphylococci, Ann. Surg. **116**:430, 1942.

446. Caspe, S., and Hadjopoulos, L. G.: Sodium Hexametaphosphate as Anticoagulant: Preliminary Study, Am. J. Pharmacol. **114**:175, 1942.

447. Smith, H. P., and Warner, E. D.: Vitamin K: Clinical Aspects, in Symposium on the Biological Action of the Vitamins, Chicago, University of Chicago Press, 1942, p. 211.

448. MacCorquodale, D. W.: Vitamin K, in Symposium on the Biological Action of the Vitamins, Chicago, University of Chicago Press, 1942, p. 202.

by D'Alessandro,[449] who recommends that all patients undergoing surgical operation on the biliary tract have a prothrombin determination without regard to the presence or the absence of jaundice. Two brief reviews of the use of vitamin K are presented by Karabin [450] and Covintree.[451]

(*a*) Hepatic Disease: The physiology of plasma prothrombin and its relation to disease of the liver are reviewed, and 117 references listed, by Andrus and Lord.[452] Abbott and Holden [453] studied 120 patients with hypoprothrombinemia before the oral administration of menadione and twenty-four to forty-eight hours later. In patients with severe hepatic damage little or no response to 8 mg. of menadione was noted, while those with obstruction of the common duct practically always showed a rise in the prothrombin value. In patients with burns the response of the prothrombin time to administration of vitamin K was suggested as an early and accurate guide to prognosis. Allen and Julian [454] noted the response of the blood prothrombin to vitamin K therapy in 57 cases of obstructive jaundice and advanced disease of the liver. The prothrombin level rose to normal in twenty-four hours in every case of obstructive jaundice following either oral administration of 8 mg. of menadione and 2.5 Gm. of bile salts or parenteral injection of 10 mg. of the water-soluble compound tetra-sodium 2-methyl-1, 4-naphthoquinone diphosphoric acid ester (synkovite-Roche). In 31 instances of advanced disease of the liver the depressed prothrombin level was either not affected or elevated only slowly by similar therapy. Histologic observation of the livers of 17 patients coming to necropsy indicated no correlation between the extent of hepatic damage and either the initial response of the prothrombin level to vitamin K therapy or the rate or the degree of this response. The author concluded that deficiency of prothrombin is not a reliable measure of hepatic function, as it does not reflect the extent of hepatic damage. In a larger group of 42 patients Sweet, Lucia and Aggeler [455] found a fairly close clinical-pathologic correlation between hepatic damage and concentration of prothrombin in the plasma. In general, the value for prothrombin was normal by the Quick technic when there was little or no destruction of parenchymal tissue and was diminished with moderate or extensive destruction of the liver. In 2 cases deviation from this rule was noted; in the first, a case of extensive destruction of the liver from an infiltrating hepatoma, the concentration of prothrombin was 70 per cent of normal, and in the second, with only slight leukemic infiltration of the liver, the prothrombin content ranged from 40 to 20 per cent of normal. The authors felt that a better correlation occurred between the prothrombin time and the histologic appearance of the liver than between the former and the excretion of hippuric acid in Quick's test. Of the two tests, the concentration of prothrombin was thought to be the less sensitive indicator of hepatic function but the more accurate detector of destruction of hepatic parenchyma. One hundred unselected

449. D'Alessandro, A. J.: Vitamin K and Its Role in Blood Coagulation, Am. J. Surg. **57**:104, 1942.

450. Karabin, J. E.: Vitamin K in Hypoprothrombinemia, Illinois M. J. **81**:56, 1942.

451. Covintree, G. E.: Vitamin K, with Special Reference to Clinical Use, Hahneman. Monthly **77**:83, 1942.

452. Andrus, W. deW., and Lord, J. W., Jr.: The Physiology of Plasma Prothrombin and Its Relation to Liver Function, Surgery **12**:801, 1942.

453. Abbott, W. E., and Holden, W. D.: Prothrombin Test as a Diagnostic and Prognostic Aid, Arch. Surg. **45**:261 (Aug.) 1942.

454. Allen, J. G., and Julian, O. C.: Prothrombin and Hepatic Function, Arch. Surg. **45**:691 (Nov.) 1942.

455. Sweet, N. J.; Lucia, S. P., and Aggeler, P. M.: A Clinical-Pathologic Correlation Between Hepatic Damage and the Plasma Prothrombin Concentration, Am. J. M. Sc. **203**:665, 1942.

cases of disease of the liver and of the biliary tract encountered as routine diagnostic problems were studied by the Quick method of determining prothrombin by White, Deutsch and Maddock.[456] The response of the hypoprothrombinemia to administration of vitamin K was compared as a test of hepatic function with the oral hippuric acid test, the fractional elimination of bromsulfalein and the excretion of urinary urobilinogen. The correlation between the prothrombin time and the results of these tests for hepatic function was poor. The excretion of hippuric acid proved a more reliable means of revealing hepatic insufficiency than did the prothrombin response to vitamin K therapy. Abnormal excretion of hippuric acid was noted in 83 cases and an abnormal prothrombin level before and after therapy was seen in 53. The prothrombin level proved inferior to the other tests as a guide to prognosis. A normal value for plasma prothrombin was misleading, but a depressed value was significant, and a failure to respond to vitamin K proved a progressively unfavorable sign. Bleeding in the cases of hepatic cirrhosis encountered by these authors was due as frequently to ruptured varices as to a low level of prothrombin. Stein [457] reports studies that confirm the rise in the blood prothrombin following parenteral injection of vitamin K in obstructive jaundice and the lack of this response in extensive disease of the liver. Owen [458] states that when the administration of vitamin K is ineffective in correcting depression of the prothrombin level it may be reasonably assumed that there is impairment of hepatic function but that the prothrombin determination reflects pathologic changes in the liver only when the damage is extreme.

Kapnick, Stewart and Lyons [459] measured hepatic function by the Quick method, the van den Bergh reaction and the bromsulfalein test in 68 patients who were receiving sulfanilamide derivatives. During the course of the chemotherapy 14 patients showed an appreciable increase in prothrombin time, and several of these patients manifested abnormalities by the other tests. No patient, however, showed an abnormal excretion of bromsulfalein or an increase of bilirubinemia without also showing a fall in prothrombin. The severity of the infection appeared to be more significant as a cause of the depression of prothrombin than the type of drugs used, but the authors suggested that change in the prothrombin level may be used as an early indication of impending damage of the liver during therapy with sulfanilamide derivatives. Definite deficiency of prothrombin was seen in 14 of 26 cases of disorders of the liver and biliary tract by Bechgaard.[460] Quick's method as modified by Lehmann was recommended as an easy and reliable test for clinical use.

The one stage method of Quick was compared with the two stage technic of determining prothrombin time in patients with hepatic disease by Ziffren, Owen, Warner and Peterson,[461] who found the latter procedure the more sensitive index

456. White, F. W.; Deutsch, E., and Maddock, S.: Comparison of Blood Prothrombin Levels with Standard Function Tests in Diseases of the Liver, New England J. Med. **226**:327, 1942.

457. Stein, H. B.: Distinction Between "Surgical" and "Medical" Jaundice by Effect of 2-Methyl-1,4-Naphthoquinone (Kapilin) on Plasma Prothrombin, South African M. J. **16**: 12, 1942; Effects of 2-Methyl-1,4-Naphthoquinone on Clotting Factors of Blood of Jaundiced Patients with Hypoprothrombinemia, South African J. M. Sc. **7**:72, 1942.

458. Owen, C. A.: Plasma Prothrombin: An Index of Liver Function, Harper Hosp. Bull. **1**:113, 1942.

459. Kapnick, I.; Stewart, J. D., and Lyons, C.: Plasma, Prothrombin and Liver Function During Sulfonamide Therapy, New England J. Med. **227**:944, 1942.

460. Bechgaard, P.: Plasma Prothrombin and Vitamin K Deficiency in Diseases of Liver and Pancreas and in Diarrheas, Ugesk. f. læger **103**:1523, 1941.

461. Ziffren, S. E.; Owen, C. A.; Warner, E. D., and Peterson, F. R.: Hypoprothrombinemia and Liver Function, Surg., Gynec. & Obst. **74**:463, 1942.

of hepatic damage. Two patients in thyroid crisis were studied, and reduction of prothrombin was found in both instances.

(*b*) Miscellaneous Disorders: The hemorrhagic tendency in sprue, due to hypoprothrombinemia, is believed by Alper [462] to result from a deficiency of intake, an increase of excretion and a failure of absorption of the fat-soluble vitamin K. The incidence of hypoprothrombinemia in certain tropical diseases is discussed by Diaz y Rivera and his associates,[463] who studied 12 patients with the hepatosplenic type of infection with Schistosoma mansoni and observed that, although 8 of them gave a history of hematemesis, no hemorrhagic tendency was apparent despite moderate prolongation of the prothrombin time. Page and Bercovitz [464] used a modification of the Quick method in studying the prothrombin of 21 patients with chronic ulcerative colitis. Six of the patients were found to have constant hypoprothrombinemia, and 13 had values fluctuating between normal and low levels. Eleven of these patients were found to have values for plasma fibrinogen slightly above normal.

Purpura due to deficiency of vitamin K in cases of anorexia nervosa was noted by Aggeler, Lucia and Fishbon,[465] who feel that the deficiency was due either to an exogenous dietary lack or to hypermotility of the gastrointestinal tract, although in no instance has hypoprothrombinemia been established to arise on the basis of purely functional disturbance of the intestinal tract.

Warner and Owen [466] used the two stage method of determining the prothrombin time in 20 cases of pernicious anemia, and found values below 50 per cent of normal in 10 and values of 75 per cent or more in only 3. Vitamin K was ineffective in altering the prothrombin level, but a rise occurred following the institution of liver therapy. Values determined by the Quick method were normal in all cases and were not modified by liver therapy. The reason for the difference in the results obtained by the two methods is not clear, but the prolongation of the prothrombin time as measured by the two stage method is not apparently related to the anemia or to its degree, and the response to liver therapy is confined to cases of pernicious anemia.

Levy [467] determined the bleeding time, the coagulation time, the prothrombin time and the degree of hepatic function in 60 cases of pulmonary tuberculosis. The Quick method and the bedside procedure of Smith revealed hypoprothrombinemia in 32 per cent of the patients, with the lowest values observed in those with pulmonary hemorrhage. In 14 patients experiencing pulmonary bleeding, varying in degree from streaked sputum to frank hemoptysis, the hemorrhage was promptly controlled by the administration of vitamin K. Serial determinations of prothrombin made on 12 tuberculous patients who had undergone thoracoplasty are reported by Savacool and Chodoff.[468] By the Quick technic a sharp drop was observed within one to two days after operation, with a lapse of one week or

462. Alper, J. M.: The Hemorrhagic Tendency in Sprue, Rev. Gastroenterol. **9**:340, 1942.

463. Diaz y Rivera, R. S.; Suarez, R. M., and Hernandez Morales, F.: Hypoprothrombinema Incident to Tropical and to Non-Tropical Diseases, Bol. Asoc. méd. de Puerto Rico **34**:177, 1942.

464. Page, R. C., and Bercovitz, Z.: Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis, Am. J. Digest. Dis. **9**:419, 1942.

465. Aggeler, P. M.; Lucia, S. P., and Fishbon, H. M.: Purpura Due to Vitamin K Deficiency in Anorexia Nervosa, Am. J. Digest. Dis. **9**:227, 1942.

466. Warner, E. D., and Owen, C. A.: Hypoprothrombinemia in Pernicious Anemia, Am. J. M. Sc. **203**:187, 1942.

467. Levy, S.: Vitamin K in Tuberculosis, with Special Reference to Pulmonary Hemorrhage, Am. Rev. Tuberc. **45**:377, 1942.

468. Savacool, J. W., and Chodoff, R. J.: Plasma Prothrombin in Tuberculous Patients: Effect of Surgical Collapse, Am. Rev. Tuberc. **46**:432, 1942.

more before the preoperative level was regained. Vitamin K was ineffective in altering the hypoprothrombinenemia of these patients, but a late spontaneous rise followed successful collapse therapy.

Dietz [469] reports that parenteral administration of vitamin K proved very effective in correcting menorrhagia and metrorrhagia. Schaad [470] used injections of vitamin K and of calcium in the successful treatment of a severe form of rheumatic purpura. Neither of these authors report determinations of prothrombin before or after vitamin K therapy.

(*c*) Pregnancy and the Neonatal Period: The administration of soluble pentobarbital U. S. P. or of sodium amyl bromoallylbarbiturate as an analgesic during labor was found by Fitzgerald and Webster [471] to lower the prothrombin level in the blood of both mother and child. Vitamin K administered during labor prevented this fall, and no neonatal hemorrhage was observed in 641 babies born of mothers so treated. A large number of infants born into families representing the lowest income group of a metropolitan area were studied by Parks and Sweet [472] for evidence of gross hemorrhage in the neonatal period. It was assumed that dietary deficiencies would be maximal in this group and that any procedure directed toward reduction of bleeding in the newborn should produce greatest benefits in such patients. On admission to the hospital in labor, the mothers of 1,151 infants were given by mouth 5 mg. of menadione, whereas another group, consisting of the mothers of 1,594 infants, received no vitamin K. Only severe hemorrhages, such as melena neonatorum, hematemesis, gross subcutaneous, cutaneous or definite intracranial hemorrhage or hemorrhage into the adrenal glands, were considered. The incidence of such bleeding was 1.4 per cent in the control group and 1.7 per cent in the infants whose mothers had received vitamin K.

The incidence of hemorrhagic manifestations in a group of 711 newborn babies who were given 1 mg. of vitamin K orally as soon as they reached the nursery was compared with that in a control group of 982 infants by Sanford, Shmigelsky and Chapin.[473] All the infants were examined daily and determinations of prothrombin made by the Quick method for at least five consecutive days after birth. In the untreated newborn infants the prothrombin levels fell rapidly throughout the first, second and third days of life and rose abruptly during the fourth to seventh days before reaching a stationary level. In the infants given vitamin K immediately after birth, no decrease was observed in the prothrombin on the first or the second day of life. Except for a slight transient decline on the third day, the prothrombin values throughout the neonatal period were about 10 per cent above those of cord blood obtained at birth. The incidence of hemorrhagic manifestations was the same in the treated and the untreated group, amounting to 6.6 per cent. Conjunctival, vaginal, petechial, cerebral and umbilical hemorrhage, melena and cephalhematoma occurred as many times in one group as in the other and the mortality percentage was the same for the two groups. The authors believe that the hemorrhagic manifestations noted differed from true hemorrhagic dis-

469. Dietz, R.: Ueber die Wirkung von Vitamin K bei Meno-und Metrorrhagien, München. med. Wchnschr. **88**:1009, 1941.

470. Schaad, H.: Vitamin K in einem schweren Fall von Purpura rheumatica, Schweiz. med. Wchnschr. **71**:1622, 1941.

471. Fitzgerald, J. E., and Webster, A.: Obstetric Significance of Barbiturates and Vitamin K, J. A. M. A. **119**:1082 (Aug. 1) 1942.

472. Parks, J., and Sweet, L. K.: Does Antenatal Use of Vitamin K Prevent Hemorrhage in the Newborn Infant? Am. J. Obst. & Gynec. **44**:432, 1942.

473. Sanford, H. N.; Shmigelsky, I., and Chapin, J. M.: Is Administration of Vitamin K to the Newborn of Clinical Value? J. A. M. A. **118**:697 (Feb. 28) 1942.

ease of the newborn. In no instance was the coagulation time of whole blood increased beyond five minutes. The incidence of cerebral hemorrhage likewise was similar in the two groups, and the authors add that they have never observed cerebral hemorrhage in the newborn associated with hemorrhages elsewhere in the body or with prolongation of the whole blood coagulation time.

A review of the role of vitamin K in blood coagulation is given by Sage.[474] This author quotes Quick's comments on the paper of Sanford and collaborators. To call attention to the fact that hemorrhage in the newborn may occur from causes other than deficiency of prothrombin is a valuable contribution, in Quick's opinion, but Quick takes sharp issue with the authors if they are attempting to depreciate the use of vitamin K in preventing and treating hemorrhagic disease of the newborn. Waddell [475] takes the same view and states that vitamin K is efficient in the treatment and especially in the prevention of this dread disease of the newborn. In England, MacPherson and Henderson [476] and Capon [477] answer Sanford and associates in a similar vein.

Inasmuch as acute hypoprothrombinemia is the only condition of the newborn that responds to vitamin K, Kugelmass [478] feels that routine administration of this vitamin is wasteful in 99.5 per cent of infants so treated. If the latent hemorrhagic tendency present in the remaining 0.5 per cent becomes active, the rise in clotting time will indicate a decrease of available prothrombin, which then is a clear indication for vitamin K therapy. In a round table discussion of hemorrhage in the newborn Poncher [479] states that alterations in the walls of blood vessels constitute the most common cause of spontaneous bleeding in the neonatal period and that hypoprothrombinemia follows next in importance. In cases of spontaneous bleeding values below 20 per cent of the normal adult value when obtained by the Quick method are considered significant, but in the presence of vascular damage values ranging from 20 to 40 per cent of normal may play an important role in conditioning bleeding.

The increased incidence of hemorrhagic disease of the newborn in the winter and early spring is pointed out by Waddell,[480] and an identical seasonal increase in deaths from intracranial hemorrhage in the neonatal period has been found in the United States during a ten year period. Approximately one-third more infants died of this complication in the winter and spring months than during any other calendar month. Quick [481] feels that the incidence of intracranial hemorrhage is reduced and that other types of obscure bleeding, such as retinal, may be largely prevented by administration of vitamin K. The successful elevation of the prothrombin level of the newborn by administration of vitamin K to the mother or to the child is reported by Reiss and Schonberger.[482]

474. Sage, E. C.: Clinical Evaluation of Vitamin K in Obstetrics, Nebraska M. J. **27**:314, 1942.

475. Waddell, W. W.: Vitamin K for the Newborn, J. A. M. A. **118**:1389 (April 18) 1942.

476. MacPherson, A. I. S., and Henderson, J. L.: Doubts on Vitamin K for the Newborn. Lancet **1**:546, 1942.

477. Capon, N. B.: Doubts on Vitamin K for the Newborn, Lancet **1**:602, 1942.

478. Kugelmass, I. N.: Vitamin K for the Newborn, J. A. M. A. **118**:1389 (April 18) 1942.

479. Poncher, H. G.: The Physiology of the Blood in the Newborn Infant, J. Pediat. **20**:637. 1942.

480. Waddell, W. W., Jr.: Hypoprothrombinemia and Hemorrhage in the Newborn Infant, J. Pedint. **20**:656, 1942.

481. Quick, A. J.: Hemorrhagic Disease of the Newborn, Marquette M. Rev. **6**:160, 1942.

482. Reiss, W., and Schonberger, R.: The Prothrombin Level in Newborn, as Influenced by Administration of Vitamin K to the Mother and to the Child, Klin. Wchnschr. **21**:319, 1942.

The effect of prelactation feedings on prothrombin deficiency in the newborn was studied by Richdorf and Kearney.[483] In a group of infants given feedings of calcium caseinate or a 5 per cent solution of casein hydrolysate every four hours prior to the first breast feeding, the prothrombin level fell less than in infants starved for a similar twelve hour period after birth.

The prothrombin time of the neonatal period was studied by MacPherson [484] in relation to the mother's dietary intake of vitamin K during pregnancy. Uniformly low prothrombin times were found for children born of mothers whose diets were inadequate in green vegetables, milk, butter, meat, fats or cereals. Four hydrocephalic infants were given at birth a diet consisting solely of dextrose and water. On this vitamin K–free diet the infants showed an initial drop in prothrombin content comparable to that of normally fed newborn infants. In contrast to normal infants, they showed a further fall in place of the expected rise in prothrombin usually seen. This was considered by the author as evidence that the synthesis of vitamin K by the bacterial flora alone is insufficient as a source of supply to meet minimal physiologic requirements. Spontaneous bleeding did not occur in these infants despite the fall of prothrombin at the end of ten days to levels which are usually associated with the onset of hemorrhagic disease in the newborn.

Three newborn infants, one with atresia of the esophagus, a second with atresia and fistula from the esophagus to the bronchus and a third with complete obliteration of the gallbladder and the extrahepatic ducts, were followed during life with serial prothrombin determinations by Sanford and Shmigelsky.[485] The first infant received fluids by injection but neither of the infants with atresia of the esophagus received food by mouth. A prothrombin determination in the case of the first child on the fifth day of life was normal for a newborn infant but, owing to subsequent blood transfusion, no further tests were made in this case. The second child gave a prothrombin curve identical with that of a normal newborn infant up to the time of death on the twelfth day. In the third infant, with complete obliteration of the gallbladder and the extrahepatic ducts, a prothrombin level obtained on the eighth day of life corresponded closely to that of a normal newborn infant. This child never received vitamin K, bile salts or blood transfusions and at the age of 4 months had a prothrombin value of 95 per cent of normal by the Quick method. The last determination made before the child's death at 6 months of age showed a drop to 75 per cent of normal. By the two stage method, however, the plasma prothrombin was considerably below normal, ranging from 32 to 48 per cent, from the first to the sixth month of life. The authors feel that these observations are not compatible with the view that the synthesis of vitamin K by bacteria from food in the small intestine demands the presence of bile for the conversion of vitamin K. The liver may be the principal source of this vitamin, they suggest, and may continue to form vitamin K independently of an extrinsic supply until function of the liver is diminished by serious damage.

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483. Richdorf, L. F., and Kearney, W.: Prothrombin Deficiency in the Newborn as Affected by Vitamin K and by Prelacteal Feeding, Journal-Lancet **62**:155, 1942.

484. MacPherson, A. I. S.: Observations on the Aetiology and Prophylaxis of Prothrombin Deficiency and Haemorrhagic Disease in the Newborn, J. Obst. & Gynaec. Brit. Emp. **49**:368, 1942.

485. Sanford, H. N., and Shmigelsky, I.: Is Presence of Bile and Food in Small Intestine Necessary for Formation of Prothrombin? Studies on Three Infants, One with Congenital Absence of Gallbladder and Extrahepatic Ducts and Two with Congenital Atresia of Esophagus, Am. J. Dis. Child. **63**:894 (May) 1942.

Hypoprothrombinemia in congenital pyloric stenosis is discussed by Wallgren.[486] He reports that a hemorrhagic diathesis seen in this disease was successfully managed by administration of vitamin K.

Percutaneous administration of vitamin K was used by Vollmer, Abler and Altman [487] in the treatment of newborn infants. The speed of absorption appeared not inferior to that with oral administration and probably was superior to that with intramuscular injection of solutions in oil. The simplicity of this method of administration was hoped by the authors to lead to general use of vitamin K in the management of all newborn infants. Menadione, dissolved in a mixture of 80 parts liquid petrolatum and 20 parts kerosene so that 1 mg. was contained in 0.1 cc. of the solution, was applied in this approximate dose (4 drops) to the chest and proved safe and reliable in the prevention of physiologic hypoprothrombinemia of the newborn. A dermatitis resulting from topical application of 1 per cent menadione in an ointment base was noted in 5 of 9 adult patients by Page and Bercovitz.[488] Only after several applications did pruritus and erythema appear, and in 1 case chronic eczematoid dermatitis ensued. In a series of 24 newborn infants with whom this method was used, there was no evidence of contact dermatitis. The specially prepared ointment base was not responsible, as patch tests with the base alone were uniformly negative.

(*d*) Experimental Hypoprothrombinemia: Rats fed a diet containing a synthetic fat, largely dihydroxystearic acid, exhibited prolongation of clotting time, according to Lockhart, Sherman and Harris,[489] who found that addition of vitamin K to the diet prevented the development of this deficiency syndrome.

Evidence suggesting that the placenta is unusually sensitive to deprivation of vitamin K is presented by Moore and collaborators.[490] Rabbits were found to abort following ingestion of a diet deficient in vitamin K but adequately supplied with all other accessory factors, including vitamin E. Postmortem study showed retroplacental hemorrhages as the only evidence of a hemorrhagic diathesis. In these experiments the plasma prothrombin time did not reach levels usually indicative of critical hypoprothrombinemia.

Obstructive jaundice was produced experimentally in rabbits by Dyckerhoff and Marx,[491] who studied the prothrombin time and its response to the administration of vitamin K. Urnas,[492] by using a technic which practically eliminated trauma to the liver, excluded this organ from the circulation of cats and rats and observed in every instance rapid fall in the prothrombin level. The author either ligated the portal vein and the hepatic artery directly or first ligated the celiac artery and the mesenteric vessels to avoid stasis in the splanchnic region. The entire bowel except the duodenal stump, the common bile duct and the rectum were moved, thus leaving the liver in situ with the hepatic veins intact. The

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486. Wallgren, A.: Hämorrhagische Diathese bei kongenitaler Pylorusstenose (Hypoprothrombinämie), Monatschr. f. Kinderh. **86**:32, 1941.

487. Vollmer, H.; Abler, C., and Altman, H. S.: Percutaneous Administration of Vitamin K, Am. J. Dis. Child. **64**:462 (Sept.) 1942.

488. Page, R. C., and Bercovitz, Z.: Dermatitis from Topical Application of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Analogue), Am. J. M. Sc. **203**:566, 1942.

489. Lockhart, E. E.; Sherman, H., and Harris, R. S.: Dihydroxy-Stearic Acid and Vitamin K Deficiency, Science **96**:542, 1942.

490. Moore, R. A.; Bittenger, I.; Miller, M. L., and Hellman, L. M.: Abortion in Rabbits Fed Vitamin K Deficient Diet, Am. J. Obst. & Gynec. **43**:1007, 1942.

491. Dyckerhoff, H., and Marx, R.: Ueber die Natur der hämorrhagischen Diathese bei Cholämie, Biochem. Ztschr. **311**:1, 1942.

492. Urnas, B.: Plasma Prothrombin Level in Cats and Rabbits After Excluding Liver from Circulation, After Stimulation of Splanchnic Nerve and After Intravenous Injection of Adrenalin, Acta physiol. Scandinav. **3**:97, 1942.

animals survived only a few hours, but with evisceration alone no fall in plasma prothrombin occurred during a period of six to eight hours. By means of an Eck fistula, the portal blood was conveyed past the liver, and in animals thus prepared the prothrombin fell within two to four hours after operation and the decline was progressive until death ten to fifteen hours later. Transient increases in prothrombin were observed in cats under ether anesthesia after intravenous administration of epinephrine hydrochloride and after electrical stimulation of the splanchnic nerve.

The rare earths lanthanum, cerium and samarium were found by Vinche and Schmidt [493] to act as antiprothrombins, their effects being similar to those noted in previous studies with neodymium and praseodymium. Beaser, Segel and Vandam [494] injected the salts of the rare earths neodymium, lanthanum and cerium intravenously into rabbits and man. The clotting time could be prolonged to the point of incoagulability. Toxic manifestations consisting of chills, fever, cramps, hemoglobinemia and hemoglobinuria were observed. The authors concluded that these side effects rendered use of the salts as anticoagulants inexpedient.

(*e*) Methods for Determining Prothrombin: The determination of the coagulation time of recalcified oxalated blood plasma is a simple and serviceable test for vitamin K deficiency, according to Cheney,[495] who points out that the tests for the prothrombin time advocated by others do not take into account the concentration of anticoagulant substances in the blood. The plasma coagulation time represents the resultant effect of the clot-promoting substances and the clot-retarding elements in a given plasma, and when an imbalance exists because of prothrombin deficiency, the clotting time is prolonged. Similar prolongation might occur with deficiency of thromboplastin, independent of vitamin K, but in clinical practice such a state occurs rarely and then only in the presence of severe thrombopenia. A standardized technic for determining the plasma coagulation time is presented.

By placing special emphasis on the difference between the prothrombin time of undiluted plasma and that of plasma diluted 25 per cent, certain abnormalities of the blood are revealed which are not shown by whole or by diluted plasma alone, according to Shapiro and collaborators,[496] who state that the absolute difference of the two determinations is a more reliable guide to prothrombin activity than either the prothrombin time of whole or that of diluted plasma alone. This conclusion was based on evidence that the difference between the prothrombin times of whole and diluted plasma varies inversely with the concentration or the activity of the prothrombin. Following administration of dicoumarin, a point is reached at which the prothrombin time of diluted plasma is substantially prolonged while that of undiluted plasma is only moderately extended. The determination of this difference is suggested as a useful procedure in the treatment of patients with dicoumarin as well as in the detection of the possible liberation into the circulating blood of an anticoagulant in certain other pathologic conditions. If dilution of these anticoagulant substances renders them ineffective, the prothrombin time of diluted plasma may be as short or even shorter than normal in spite of a lengthened prothrombin time of whole blood.

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493. Vinche, E., and Schmidt, E.: The Effects of the Rare Earth Salts on Prothrombin and Their Influence on Vitamin K$_2$, Ztschr. f. physiol. Chem. **273**:39, 1942.

494. Beaser, S. B.; Segel, A., and Vandam, L.: The Anticoagulant Effects in Rabbits and Man of the Intravenous Injection of Salts of the Rare Earths, J. Clin. Investigation **21**:447, 1942.

495. Cheney, G.: The Normal Plasma Coagulation Time, Am. J. M. Sc. **203**:325, 1942.

496. Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: Procedure and Clinical Interpretations, Proc. Soc. Exper. Biol. & Med. **50**:85, 1942.

A detailed account of the technic of estimating prothrombin by the use of Russell's viper venom and lecithin in place of tissue thromboplastin extracts is given by Witts and Hobson,[497] together with the normal range of variation expected with this method. Witts [498] found that the difference between the coagulation times obtained with venom and with venom plus lecithin is inversely proportional to the number of platelets present in the plasma. A high difference with lecithin was noted in thrombopenia and thrombasthenia. In patients under dicoumarin therapy the difference with lecithin increases as the prothrombin is reduced. Further application of the difference with lecithin may serve as a method for the detection on inhibitor and accelerator substances in blood coagulation. Viper venom and lecithin are thought by Macfarlane [499] to be more reliable than animal tissue as a source of thromboplastin. The enzyme factor thrombokinase is supplied by the venom, and the lipoid factor, present in animal thromboplastin, by lecithin. Page, de Beer and Orr [500] studied the method in 30 subjects and found that venom alone revealed certain prothrombin deficiencies not evident with lecithinized venom. The use of lecithinized venom offered a valuable adjunct, which may become more important as the difference between the two clotting times is better understood.

Current methods for estimating the prothrombin content of whole blood and plasma are reviewed by Warner.[501] The micro adaptations in use compare favorably in accuracy with the macro types of procedure. In cases of pernicious anemia in relapse or in cases of hepatic disease the results of the one stage method are not in agreement with those of the two stage technic. The two stage method has the advantage of eliminating the influence of factors which alter the speed of the conversion of prothrombin to thrombin.

Methods for performing microprothrombin determinations on whole capillary blood under standard physical conditions are described by Hoffman and Custer.[502] Other technics suitable for bedside prothrombin tests are described.[503]

(*f*) Substances Possessing Vitamin K Activity: The water-soluble tetra sodium salt of 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester was found by Davidson, Steigman and Udesky [504] to be more active on a molecular basis than menadione. By parenteral administration of it in 10 mg. doses a satisfactory response was obtained in patients with hypoprothrombinemia in twenty-four to forty-eight hours. The toxicity of menadione and some related compounds was

497. Witts, L. J., and Hobson, F. C. G.: Estimation of Prothrombin with Venom and Lecithin, Brit. M. J. **1**:575, 1942.

498. Witts, L. J.: Disturbances in the Coagulation of the Blood (Finlayson Memorial Lecture), Glasgow M. J. **137**:57, 1942.

499. Macfarlane, R. G.: Vitamin K and Estimation of Prothrombin, Proc. Roy. Soc. Med. **35**:410, 1942.

500. Page, R. C.; de Beer, E. J., and Orr, M. L.: Prothrombin Studies Using Russell Viper Venom: Effect of Lecithinized Venom on Prothrombin Clotting Time, J. Lab. & Clin. Med. **27**:830, 1942.

501. Warner, E. D.: Current Methods for Estimating Prothrombin, West. J. Surg. **50**:408, 1942.

502. Hoffman, O. D., and Custer, R. P.: A Micro Method for Determining Prothrombin Time on Fresh Capillary Blood Using Standard Physical Conditions, Am. J. M. Sc. **204**:420, 1942.

503. Lufkin, N. H., and Strolberg, M.: A Simplified Prothrombin Test, Am. J. Clin. Path. (Tech. supp.) **6**:64, 1942. Abramson, D. J., and Weinstein, J. J.: A Rapid Bedside Micro-Prothrombin Test, ibid. **6**:1, 1942. Ulin, A. W., and Barrows, E.: A New Presumptive Test for Prothrombin Determination, J. A. M. A. **120**:826 (Nov. 14) 1942. Rhorer, A.: A One-Minute Bed-Side Prothrombin Method, Am. J. Clin. Path. (Tech. supp.) **6**:51, 1942.

504. Davidson, M.; Steigman, F., and Udesky, H. L.: Clinical Studies on the Anti-Hemorrhagic Effects of a New Water-Soluble Vitamin K-like Substance, Surg., Gynec. & Obst. **74**:35, 1942.

investigated in animals by Ansbacher, Corwin and Thomas.[505] An amount of menadione one hundred and twenty-five times the maximal clinical dose proved noninjurious even on repeated administration.

Alcoholic extracts of European mountain ash berry (Sorbus aucuparia L.) proved effective in correcting abnormal clotting time in chicks with experimental hemorrhagic hypoprothrombinemia. Shinowara, DeLor and Means [506] administered such an extract (sorparin) orally to 14 patients with biliary or hepatic disease and noted satisfactory elevations of the depressed prothrombin level in a majority of them, and symptomatic improvement when it was administered in conjunction with bile salts, beyond that ordinarily produced by other materials possessing vitamin K activity.

Menadione, unlike vitamin K, when added to whole blood in vitro caused the formation of methemoglobin. Scudi [507] found that menadione was rapidly converted to some other substance or substances which contained little of its original antihemorrhagic activity.

In a group of mice with induced hypoprothrombinemia, Barnes [508] found that daily intraperitoneal injection of 0.1 cc. of a 1 per cent solution of congo red over a period of three to eight days raised the plasma prothrombin level 23 per cent.

Hypoprothrombinemia was induced in rats by a diet containing 20 per cent liquid petrolatum by Grodins and Ivy.[509] When to these prothrombin-deficient animals 500 to 1,000 units of vitamin D was administered subcutaneously, elevation of the prothrombin level was observed in only a few cases. The failure of vitamin D to alter hypoprothrombinemia in experimental animals has been reported by others.

(*g*) Substances Possessing Thromboplastic Activity: The thromboplastic activity of extracts of various tissues on the plasma of the same and different species of animals was studied by Copley.[510] Thromboplastins were obtained from rabbit brain, rabbit skin, chicken brain and chicken skin. A trend toward species specificity was noted in general and was seen in particular with chicken plasma. Neither of the chicken thromboplastins exhibited any significant activity when tested with human plasma. In human plasma the extract of rabbit brain accelerated the prothrombin time to a greater degree than the extract of rabbit skin.

Instead of expressing the accelerating effect of the thromboplastin emulsion on the coagulation time of oxalated plasma in seconds, the authors introduce a "thromboplastic coefficient." This coefficient expresses the ratio of the coagulation time of recalcified plasma to the prothrombin time and gives a value of 1 if the added emulsion does not exhibit any activity. During the course of the study it became apparent that the widely accepted explanation of the phenomena of the prothrombin time based on the Morawitz concept of blood coagulation could not be correlated with the present finding. The discrepancy in the pro-

505. Ansbacher, S.; Corwin, W. C., and Thomas, B. G. H.: Toxicity of Menadione, Menadiol and Esters, J. Pharmacol. & Exper. Therap. **75**:111, 1942.

506. Shinowara, G. Y.; DeLor, C. J., and Means, J. W.: Clinical and Laboratory Investigations on Extract of European Mountain Ash Berry, with Particular Reference to Its Anti-Hemorrhagic Activity, J. Lab. & Clin. Med. **27**:897, 1942.

507. Scudi, J. V.: Reactions of 2-Methyl-1, 4-Naphthoquinone (Menadione) with Whole Blood and Plasma in Vitro, Proc. Soc. Exper. Biol. & Med. **50**:16, 1942.

508. Barnes, W. A.: Effect of Congo Red on Plasma Prothrombin, Proc. Soc. Exper. Biol. & Med. **49**:15, 1942.

509. Grodins, F. S., and Ivy, A. C.: Effect of Vitamin D on Prothrombin Deficiency in the Rat, Proc. Soc. Exper. Biol. & Med. **49**:439, 1942.

510. Copley, A. L.: On the Thromboplastic Activity of Brain and Skin Extracts, Am. J. Physiol. **137**:178, 1942.

thrombin time of the same plasma when various thromboplastins were employed and that between the prothrombin time and the simple coagulation time of recalcified plasma could not be explained by Quick's concept that the prothrombin time in seconds indicates the concentration of prothrombin present in the plasma. This explanation failed likewise when thromboplastins from different organs of the same species were utilized. Inasmuch as the contention that prothrombin is the precursor of thrombin is still in some doubt, it has been suggested by others that thromboplastin activates thrombin by exclusion of inhibitory substances. The latter view is incorporated by the author in the Howell theory of blood coagulation, in an effort to explain the discrepancies noted.

Mother's milk to which a small quantity of pyrrole has been added was used as a source of thromboplastin by Freudenberg [511] in determinations of prothrombin time.

(*h*) Miscellaneous Observations: A method for the quantitative measurement of antithrombin in blood was devised by Wilson.[512] Normal human plasma and serum contained similar amounts of antithrombin averaging 90 units per cubic centimeter when 1 unit is defined as that amount which will inactivate 1 unit of thrombin in four minutes at 28 C. The amount of antithrombin reported by this author is one thousand times greater than that observed with previous methods. During blood coagulation only a small portion of the thrombin is absorbed onto fibrin, the remainder being inactivated or neutralized by the antithrombic activity of the serum. In hypoprothrombinemia the presence or the absence of a hemorrhagic tendency is not fully explained on the basis of decreased prothrombin and variation in the conversion rate of prothrombin to thrombin. Normal human plasma contains 300 units of prothrombin per cubic centimeter, 1 unit being defined as that amount which when converted to thrombin will clot 1 cc. of fibrinogen in fifteen seconds. In a patient with cirrhosis of the liver accompanied by spontaneous ecchymosis and bleeding of the gums, seen by the author, the plasma prothrombin was 25 per cent of normal, or 75 units per cubic centimeter, and the antithrombin was 95 units. When the prothrombin unitage approximates or is lower than the antithrombin unitage, a hemorrhagic diathesis will usually occur.

The prothrombin content of oxalated blood stores at 0 C. was found stable for eight days by Lavergne and Lavergne,[513] who determined the prothrombin content by diluting the plasma with fresh prothrombin-free plasma prior to employing the Quick technic. The authors felt that the prolonged clotting time obtained by other workers was influenced by a diminished fibrinogen content of the stored blood. The prothrombin content of dried plasma preserved in a frozen state and then reconstituted with distilled water was shown by Strumia [514] to be only 15 to 20 per cent of normal. However, if the plasma was reconstituted with distilled water saturated with carbon dioxide, values of 50 to 60 per cent were obtained, and if 0.1 per cent citric acid was used, the values were 67 per cent of normal. The original prothrombin content of the plasma, determined before drying, was found to be 65 to 70 per cent of normal. No untoward reactions in man have followed intravenous administration of plasma regenerated with 0.1 per

511. Freudenberg, E.: Die Frauenmilchmethode zur Bestimmung der Prothrombinzeit, Schweiz. med. Wchnschr. **71**:1256, 1941.

512. Wilson, S. J.: Quantitative Studies on Antithrombin, Arch. Int. Med. **69**:647 (April) 1942.

513. Lavergne, G. H., and Lavergne, R.: The Stability of Prothrombin in Stored Blood, Compt. rend. Soc. de biol. **136**:445, 1942.

514. Strumia, M. M.: Preservation of Prothrombin in Dried Plasma, J. A. M. A. **119**: 710 (June 27) 1942.

cent citric acid. The excessive alkalinity of plasma reconstituted from the dried state is avoided, and deterioration of prothrombin is prevented, by the use of the citric acid solution. The prothrombin activity of oxalated plasma was found by Tocantins [515] to fall rapidly after the plasma had been standing a few hours uncovered and exposed to air currents. By aerating the plasma with carbon dioxide, the prothrombin activity could be restored to its initial value.

BLOOD CHANGES ASSOCIATED WITH VARIOUS DISORDERS

Blood in Infection.—The hematologic findings in 117 cases of appendicitis were analyzed by Dutton,[516] who concludes that a leukocyte count above 12,000 per cubic millimeter with 80 per cent neutrophils strongly suggests diffuse suppurative appendicitis and provides an indication for immediate surgical intervention. Less marked leukocytosis and a lower percentage of neutrophils are compatible with a diagnosis of catarrhal inflammation. When eosinophils are found in the stained blood film there is little likelihood that a suppurative process is present. The author concludes that a diagnosis of acute appendicitis is apt to be inaccurate whenever studies of the blood demonstrate no abnormalities.

After studying 250 assorted cases of arthritis Kling [517] concludes that the Weltman coagulation test does not possess the general utility of the erythrocyte sedimentation rate. The latter he believes to be superior in evaluating the clinical course, although the Weltman procedure employed as an adjunct to the sedimentation rate and the differential count may yield helpful information.

Lewis-Fanning and Myers [518] doubt that the sedimentation rate is altogether reliable in estimating the activity of a tuberculous process. It is pointed out that the laboratory procedure to obtain this rate may occasionally give a result within normal limits in the presence of actively progressing lesions. However, their studies indicate that in general the rate is of considerable prognostic value since the mortality rate of patients leaving the sanatorium with the erythrocyte sedimentation rate still elevated was considerably higher than that of the group who were discharged after the sedimentation rate had become normal.

Lockie, Sanes and Vaughan [519] define Felty's syndrome as a chronic nonspecific arthritis of adults accompanied by splenomegaly and neutrophilic leukopenia. The detailed postmortem observations in 1 case are reviewed. Histologically, the enlarged spleen demonstrated sinus endothelial hyperplasia and infiltration by plasma cells and eosinophils, whereas sections of the liver showed parenchymatous degeneration and swelling of the Kuppfer cells. Other noteworthy findings were interstitial myocarditis, thyroiditis, pancreatitis and myositis. The authors believe that these tissues demonstrated a nonspecific inflammatory reaction. The inefficacy of all forms of therapy is emphasized. Waitzkin's [520] patient derived temporary improvement following splenectomy. In a case of Felty's syndrome presented by

515. Tocantins, L. M.: Loss of Prothrombin Activity in Plasma Exposed to Air Current, Proc. Soc. Exper. Biol. & Med. **49**:251, 1942.

516. Dutton, L. O.: Blood Findings in Acute Appendicitis, Texas State J. Med. **37**:669, 1942.

517. Kling, D. H.: The Weltman Coagulation Reaction and the Sedimentation Test in Arthritis, Ann. Rheumat. Dis. **2**:256, 1941.

518. Lewis-Fanning, E., and Myers, M.: Prognostic Value of the Blood Sedimentation Rate in Pulmonary Tuberculosis, Brit. M. J. **2**:125, 1942.

519. Lockie, L. M.; Sanes, S., and Vaughan, S. L.: Chronic Arthritis Associated with Neutrophilic Leukopenia, Splenomegaly and Hepatomegaly: "Felty's Syndrome," Am. J. Clin. Path. **12**:372, 1942.

520. Waitzkins, L.: Felty's Syndrome, Virginia M. Monthly **69**:80, 1942.

Steinberg [521] splenectomy was performed after all conservative measures had failed to control the anemia. Improvement of the blood occurred, but the arthritis did not recede. Elsom and Ingelfinger [522] report their findings in 2 patients both of whom had eosinophilia of the blood, pneumonitis and laboratory findings compatible with chronic brucellosis.

Brumpt [523] points out that a parasite of rats, Hepatozoon, is exclusively phagocytosed by monocytes and that white blood cell counts of infected animals have shown the monocytes ranging from 35 to 85 per cent. The author suggests that the experimental use of this parasite might lead to a better understanding of the origin and development of the monocyte. Fatal hemolytic anemia of pigeons caused by Plasmodium relictum (a parasite of birds resembling that causing malaria) is reported by Hill.[524]

Nephritis.—Anemia as seen in 36 children with nephritis is analyzed by MacArthur.[525] The group consisted of 21 children with acute nephritis, 5 with the nephrotic syndrome, 5 with nephrosclerosis (chronic interstitial) and 5 with chronic hemorrhagic nephritis. Only in those with chronic hemorrhagic nephritis was true anemia found. It was characterized by an orthochromic, normocytic blood picture with a normal or slightly increased number of reticulocytes and associated mild leukocytosis. Iron therapy was without effect on the anemia. The author believes that the anemia is not due to hypoplasia of the bone marrow, for it is not associated with diminution of the number of white blood cells or of that of reticulocytes. In the absence of complicating hemorrhage, no anemia was found in the children with nephrosclerosis. In the children with the nephrotic syndrome, hemoconcentration reached its maximum during the period of oliguria, but slight anemia was occasionally present. In the children with acute nephritis hemoconcentration was at its height during active diuresis. Our experience indicates that in advanced glomerular nephritis with azotemia, and occasionally in nephrosclerosis with absolute renal insufficiency, selective impairment of erythropoiesis occurs, the block appearing very early in the development of the red blood cells. Only in this sense can the resulting anemia be designated as hypoplastic. In patients with nephrosis, mild to moderate anemia, often macrocytic, may be attributable to alterations in protein metabolism.

Chemical Intoxications.—Eleven hundred and four workers employed in the rubber industry were studied by Wilson.[526] They were exposed to benzene fumes, the concentration averaging 100 parts per million. Seven and five tenths per cent showed slight blood changes, and 2.2 per cent more pronounced changes. Of the latter group consisting of 25 persons, 9 were hospitalized; 3 of these died. The blood changes resulting from exposure to benzene fumes can be summarized as leukopenia with increase in the ratio of monocytes and decrease in the polymorphonuclear cells. The red cell count, the hemoglobin content and the platelet count were low. Aspirated marrow showed varying degrees of hypoplasia. The blood prothrombin level remained normal. The treatment recommended by the author consists of multiple small blood transfusions and infusions of 2 to 5 cc. of yellow bone marrow. Multiple vitamin therapy with intramuscular injections

521. Steinberg, C. L.: The Value of Splenectomy in Felty's Syndrome, Ann. Int. Med. **17**:26, 1942.

522. Elsom, K. A., and Ingelfinger, F. J.: Eosinophilia and Pneumonitis in Chronic Brucellosis: A Report of Two Cases, Ann. Int. Med. **16**:995, 1942.

523. Brumpt, E.: Monocytose parasitaire du rat: Son utilisation possible pour l'étude de la monocytopoiese, Compt. rend. Soc. de biol. **136**:345, 1942.

524. Hill, C. M.: Anemia as a Cause of Death in Bird Malaria, Am. J. Hyg. **36**:143, 1942.

525. MacArthur, P.: Anaemia in Nephritis, Arch. Dis. Childhood **17**:1, 1942.

526. Wilson, R. H.: Benzene Poisoning in Industry, J. Lab. & Clin. Med. **27**:1517, 1942.

of liver extract, together with oral administration of iron, calcium and phosphorus, is suggested.

Meyer and Ginsberg [527] report fatal aplastic anemia following exposure to benzene fumes. Prior to death of the patient three unsuccessful attempts were made to obtain sternal marrow. Postmortem observations are reported. An aplastic marrow was revealed.

The expected blood findings in lead poisoning are discussed by Kehoe.[528] The red cell count is likely to be decreased and perhaps low, but may be entirely normal. The hemoglobin value may show similar variations, but no characteristic change is noted in the white cell count. In most cases a significant increase in the number of stippled red blood cells in the peripheral blood is noted. The mean number of stippled cells in the blood of normal persons is given as 339.18 ± 9.72 per million red blood cells. In 30 cases of lead poisoning studied before the subsidence of an acute attack, an average of 5,856 stippled red blood cells per million was found, with a range of 720 to 16,000. In the course of an acute illness the absence of stippled red blood cells can usually be taken as convincing evidence that lead is not the responsible agent, but an exception to this rule is seen in sudden overwhelming lead intoxication. Due to the wide variation of the individual hemopoietic response to plumbism, the number of stippled red cells cannot be taken as an index to the degree of absorption of lead. A progressive increase in the stippled cells, however, is evidence of increasing intoxication by lead. On recovery from plumbism the stippled cells disappear before the concentration of lead in the blood and in the urine has returned to normal.

Matz [529] reports lead poisoning in a 20 month old child following the use of a plaster of lead oleate in the treatment of infantile eczema.

Increased numbers of stippled red blood cells were found by Abraham and Baird [530] while they were examining blood films for malaria at an army post. Investigation led to the discovery that tetraethyl lead gasoline was being used for cooking in a mess kitchen. Five of 7 men exposed to the fumes were found to excrete abnormal amounts of urinary lead. Clinical symptoms of lead intoxication developed in 2 of the 5 men, while 3 remained symptom free. The men in whom plumbism developed were cooking in a closed kitchen. In other groups, cooking with tetraethyl lead gasoline outdoors under a tent fly, no signs of lead intoxication appeared.

The origin of porphyrinuria in lead poisoning was studied by Kark and Meiklejohn.[531] The type III coproporphyrin found in the urine in plumbism has been shown to differ from the type I porphyrin which is present in several other conditions associated with porphyrinuria. This has led to the assumption that the porphyrin in lead poisoning, which is similar to the protoporphyrin of hemoglobin, is present as a consequence of alteration in the metabolism of hemoglobin. The authors gave solutions of hemoglobin intravenously to 2 patients with lead poisoning. The plasma bilirubin showed a rise resembling closely that observed

527. Meyer, L. M., and Ginsberg, V.: Aplastic Anemia, J. Indust. Hyg. & Toxicol. **24**: 37, 1942.

528. Kehoe, R. A.: Symposium on Industrial Medicine: Lead Absorption and Lead Poisoning, M. Clin. North America **26**:1261, 1942.

529. Matz, M. H.: Lead Poisoning Caused by Plaster of Lead Oleate, Diachylon: Report of a Case Occurring During the Treatment of Infantile Eczema, Arch. Pediat. **59**: 805, 1942.

530. Abraham, A. E., and Baird, J. A.: Clinical and Subclinical Lead Intoxication, War Med. **2**:450 (May) 1942.

531. Kark, R., and Meiklejohn, A. P.: Significance of Porphyrinuria in Lead Poisoning, J. Clin. Investigation **21**:91, 1942.

in normal persons, accompanied by a transient increase in urinary urobilinogen. No detectable increase in the excretion of porphyrin resulted in either the urine or the feces. The authors felt that the porphyrin observed in lead poisoning was not derived from abnormal destruction of red cells but might originate from defective synthesis of hemoglobin. The stippled red blood cells have been shown by others to contain protoporphyrin. The present authors suggest that the stippled cells are the result of faulty synthesis of hemoglobin with resulting accumulation of porphyrin in the erythrocytes. When the stippled cells are ultimately destroyed, the porphyrin, being an abnormal metabolite, is excreted in an abnormal manner. Kench, Gillam and Lane [532] take a different view of the origin of porphyrinuria in lead poisoning. They measured the amount of protoporphyrin in the blood of 12 subjects whose exposure to lead had been moderately heavy. The amount of pigment was insignificant compared with the quantity anticipated if the existing anemia was dependent on failure of iron-porphyrin formation. One of the authors ingested 20 mg. of lead acetate daily for thirty-eight days, and although urinary coproporphyrin type III reached high values the concentration of hemoglobin in the blood remained unaltered. Further, no relation was found between the degree of stippling and the concentration of protoporphyrin in the blood. The diminution in the formation of hemoglobin in plumbism, the authors suggest, is due not to nonutilization of protoporphyrin but to depression of marrow function as a result of intoxication by lead.

An excellent review of the clinical and blood changes associated with poisoning in munition workers is presented by Noro.[533] The blood dyscrasias following exposure to amatol (a mixture of trinitrotoluene and ammonium nitrate) and tetryl (tetranitromethylaniline) were found to be similar. One hundred and nine patients were studied, and anemia, normochromic or hyperchromic, was found in 43, leukopenia in 22 and leukocytosis in 13. The white cell count ranged from 2,600 to 20,300 per cubic millimeter. Thrombopenia was noted in 50 patients and thrombocytosis in 6. Poisoning following use of mercury fulminate produced anemia with a high color index and a remarkable degree of thrombocytosis, the platelet count reaching 1,240,000 per cubic millimeter in 1 instance.

No direct relation between synthesis of porphyrin and metabolism of hemoglobin was demonstrated by Bjorkman,[534] who produced experimental lead poisoning in rabbits. He feels that porphyrinuria has its origin in a disturbance in the metabolism of cytochrome. Bambach, Kehoe and Logan [535] report that 90 per cent of the total amount of lead in the blood of rabbits is found in the cellular portion after separation of the corpuscles by centrifugation.

The symptoms of chronic acetanilid poisoning are reviewed by Austin,[536] who reports the case of a 44 year old woman with chronic anemia and leukopenia due to combined acetanilid and aminopyrine poisoning. The total white cell count never exceeded 3,000 per cubic millimeter over a four year period of observation. Progressive neutropenia and splenomegaly were noted. On withdrawal of the

532. Kench, J. E.; Gillam, A. E., and Lane, R. E.: Hemopoiesis in Lead Poisoning, Biochem. J. **36**:384, 1942.

533. Noro, L.: Investigation of Trotyl, Tetryl and Fulminate of Mercury Poisoning in Munition Workers in Finland, Acta med. Scandinav. (supp.) **120**:1, 1941.

534. Bjorkman, S. E.: Coproporphyrinuria and Hemoglobin Metabolism in Experimental Lead Poisoning, Acta med. Scandinav. **108**:568, 1941.

535. Bambach, K.; Kehoe, R. A., and Logan, M. A.: The Plasma-Cell Partition of Blood Lead, J. Pharmacol. & Exper. Therap. **76**:326, 1942.

536. Austin, V. T.: Chronic Anemia and Leukopenia in Combined Acetanilid and Aminopyrine Poisoning, J. A. M. A. **120**:911 (Nov. 21) 1942.

aforementioned drugs, the blood values returned to normal and the spleen was no longer palpable. In this patient leukopenia and neutropenia followed oral administration of either aminopyrine or acetanilid. A positive intradermal test was obtained with specially prepared aminopyrine.

METHODS AND MISCELLANEOUS MATERIAL

Quantitative studies on all of the corpuscular elements of the blood of healthy young men are reported by Hamre and Au.[537] The group comprised 137 boys and men between the ages of 15 and 25 years who were residents of the Hawaiian Islands. This is the most comprehensive study of the blood values of a large group of normal persons which has been published. No age or racial differences were noted in these values, and the values reported agree closely with those which have been obtained in other parts of the world. Hicks[538] determined the hemoglobin and erythrocyte levels of 125 infants within twelve hours after birth, excluding those who were delivered prematurely. The observed range of the hemoglobin was 16.1 to 27.2 Gm. per hundred cubic centimeters, with a mean of 22.3 Gm. and a standard deviation of 2.77 Gm. The red cells ranged between 4,650,000 and 9,670,000 per cubic millimeter, with a mean of 6,950,000 and standard deviation of 950,000. The author found no correlation between the hemoglobin values and the birth weights of the infants studied. Unfortunately, he gives no information concerning a possible relation between the length of time after delivery before the cord was tied and the concentration of erythrocytes and of hemoglobin.

In order to find out whether routine determination of hemoglobin, of packed cell volume of erythrocytes, of mean corpuscular hemoglobin concentration and of sedimentation rate would yield information of sufficient clinical significance to warrant permanent establishment of such a service in a large general hospital, Sturgis and Bethell[539] carried out these procedures for almost all of the adults registering at the University Hospital, Ann Arbor, Mich., during a two week period. The blood specimens were collected with a minimum of stasis in tubes containing the dry ammonium and potassium oxalate mixture of Heller and Paul, 2 mg. of the combined salt for each cubic centimeter of blood. The hemoglobin was determined by an oxyhemoglobin photoelectric method, calibrated with the oxygen capacity method of Van Slyke; the sedimentation rate was measured by the Wintrobe and Landsberg method, Wintrobe tubes being used, in which the packed cell volumes were later determined by centrifuging at 3,000 revolutions per minute for thirty minutes. Minimum normal hemoglobin values for men and women were established, respectively, as 13.3 and 12.1 Gm. per hundred cubic centimeters. The maximum normal sedimentation for both sexes, "corrected" to a hematocrit value of 47 per cent, was assumed to be 10 mm. in one hour. Determinations were made for 763 persons, including some healthy ones, who were being examined before employment. The total percentage of abnormally low hemoglobin values was 24.26. Hypochromia, characterized by a mean corpuscular hemoglobin concentration of less than 30 per cent, was indicated by the blood values of 72.4 per cent of the anemic patients. The sedimentation rates of 48.4 per cent of the subjects exceeded 10 mm. per hour and those of 33.1 per cent 15 mm. per hour. This survey has now been established on an annual

537. Hamre, C. J., and Au, M. H.: Hematologic Values for Normal Healthy Men Sixteen to Twenty-Five Years of Age, J. Lab. & Clin. Med. **27**:1231, 1942.

538. Hicks, J. D.: Haemoglobin Values in the Blood of New-Born Infants, M. J. Australia **2**:117, 1942.

539. Sturgis, C. C., and Bethell, F. H.: The Determination of Hemoglobin, Sedimentation Rate and Packed Volume of Erythrocytes as a Routine Procedure at the Time of Hospital Registration, Univ. Hosp. Bull., Ann Arbor **8**:101, 1942.

basis, and data obtained from the examination of about 20,000 subjects will be reported at a later date.

Brückmann [540] determined the hemoglobin concentration of blood drawn from the vein, the ear and the finger for healthy and for anemic persons. The values obtained on blood from the finger and the vein agreed closely, whereas those secured on blood from the ear were significantly higher.

Hematologic values of normal male rats, including the erythrocyte count, the hemoglobin value, the reticulocyte percentage, the leukocyte count and the differential formula, are reported by Thewlis and Meyer,[541] with a statistical analysis of the data. Kindred [542] estimated for 8 young male rats the volume and the number of cells per unit volume of bone marrow, spleen, thymus, lymph nodes and Peyer's patches, together with the percentage distribution of the different types of cells, the percentage in mitosis, the rate of growth and the rate of destruction. He draws the conclusion that the myeloid elements are adequate for the maintenance of normal numbers of granulocytes but that the erythroid tissue is insufficient to account for the circulating erythrocytes and the needs of replacement unless one accepts the theory of Jordan that small lymphocytes may undergo transformation into erythroblasts.

Clegg and King [543] point out that circulating hemoglobin may be divided into two parts: (1) reduced hemoglobin and oxyhemoglobin and (2) carboxyhemoglobin and methemoglobin or sulfhemoglobin. A satisfactory method of determination should measure both portions. The author reports the use of an alkaline hematin method which accomplishes this purpose. Specially prepared hemin is employed as a standard, and the method was found to be rapid, convenient and accurate. Rimington [544] describes a method for the determination of hemoglobin in which all of the heme pigments in the blood are converted to pyridine-hemochromogen and the concentration of this substance measured in a photometer. Pure solutions of heme are readily prepared and serve as the basis for the standard. Flink and Watson [545] also employ a pyridine-ferrohemochromagen method in the determination of hemoglobin and related heme pigments in blood plasma, feces and urine. The error in recovery of added hemoglobin for urine and plasma was within 10 per cent; for feces recovery ranged between 75 and 95 per cent. The authors point out that protohematin and deuterohematin are not included in the heme pigments which are converted to pyridine-hemochromogen.

Duffie [546] has devised a pocket-sized visual photometer for the estimation of hemoglobin. An illuminant is mounted in the base of the instrument and a green filter, no. 74, is placed above the solution of oxyhemoglobin and the permanent sliding neutral gray standard. Color comparison is eliminated by this rapid and practical method, since the readings are based on the concentration of light passing through the green filter.

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540. Brückmann, G.: Blood from the Ear Lobe: Preliminary Report, J. Lab. & Clin. Med. **27**:487, 1942.

541. Thewlis, E. W., and Meyer, O. O.: Blood Count of Normal White Rats, Anat. Rec. **82**:115, 1942.

542. Kindred, J. E.: A. Quantitative Study of the Hemopoietic Organs of Young Adult Albino Rats, Am. J. Anat. **71**:207, 1942.

543. Clegg, J. W., and King, E. J.: Estimation of Haemoglobin by the Alkaline Haematin Method, Brit. M. J. **2**:329, 1942.

544. Rimington, C.: Haemoglobinometry, Brit. M. J. **1**:177, 1942.

545. Flink, E. B., and Watson, C. J.: A Method for the Quantitative Determination of Hemoglobin and Related Heme Pigments in Feces, Urine and Blood Plasma, J. Biol. Chem. **146**:171, 1942.

546. Duffie, D. H.: Elimination of Color from Visual Hemoglobinometry, J. A. M. A. **119**:493 (June 6) 1942.

According to Ponder,[547] neither acid nor alkaline hematin methods of estimating hemoglobin agree well with Wong's iron method. The errors of the hematin methods depend on the variable periods required for complete conversion of hemoglobin, and on substances other than hemoglobin in both plasma and cells which affect the color of the solution.

The total volume of circulating erythrocytes as determined with the aid of radioactive iron–tagged cells is not increased by the administration of epinephrine to human subjects, according to Ross and Chapin,[548] although they observed rises in the venous hematocrit values and the plasma protein concentration of from 4 to 6 per cent. These changes were attributed to hemoconcentration or to redistribution of cells and plasma in the vascular system.

A method of estimating the average length of life of the red cells in the circulation of rabbits is reported by Graam.[549] This procedure is based on inducing reticulocytosis by means of hemorrhage and determining the time which elapses between the reticulocyte peak and the secondary fall in the erythrocytes. By this method the author determined a duration of life of erythrocytes of six to seven days in young rabbits and about five days in older animals.

The changes in size of erythrocytes occurring after hemorrhage were measured by Brown and his associates,[550] who found minor increases after a single large hemorrhage, still smaller increases after several severe hemorrhages and no increase after repeated withdrawals of small amounts of blood. They observed no evidence indicating that swollen red cells are immobilized in the capillaries of muscles after hemorrhage or that such cells are returned to the circulation following plasma transfusion as previously described by Brennan. The authors' observations, made after single large hemorrhages in 13 human subjects, after operation in 9 cases and in 1 rabbit and 2 cats, indicated that hemodilution is complete in about twenty-four hours in normal subjects but that it may be prolonged for from three to four days after operation.

A method for determining the approximate surface area of the erythrocyte is described by Bernstein and Chesluk.[551] The procedure is based on the assumption that the erythrocyte is a flat disk rather than a biconcave structure, but by construction of a rectangle the error introduced by this assumption is largely compensated for. By this method the mean surface area of the erythrocytes of normal subjects averaged 135.44 square microns with a standard deviation of 3.517 square microns.

Cytologic changes in polymorphonuclear neutrophils occurring in toxic conditions are described by Ponder and Ponder.[552] Such changes include ameboid outline of the cell, toxic granules and vacuoles in the cytoplasm, and pyknotic areas in the nucleus. A method is devised for the qualitative grading of each cell which, according to the authors, clearly reflects the clinical condition of the patient and is more informative than the total leukocyte count, the neutrophil

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percentage, the nuclear shift or the degenerative index. E. Ponder [553] describes two types of neutrophils, the "polycyte" and the "propolycyte," in relation to the typical neutrophil, on the one hand, and the macropolycyte on the other. "Polycytes and their precursors, propolycytes, are characterized by hypersegmentation or complex nuclei, but are of usual size." Such forms are believed to result from an increase in the rate of maturation of the neutrophil series, and when seen in the course of an acute or chronic infection, are of favorable prognostic significance.

The granules of eosinophilic leukocytes have been made the subject of an investigation by Buña.[554] According to him, such granules have been believed to consist of lipids (Mosler, Pappenheim), proteins (Weiss), lipoprotein complexes (Fiessinger) and hemoglobin (Weidenreich). Barker and Petry state that the granules of the eosinophils of horse blood contain 11 per cent of iron, a finding which has been challenged by Marwedel and Askanazy. Liebereich has classified the granules of the eosinophils into two groups: (1) the A granules, which are soluble in acetic acid; (2) the A′ granules, which are resistant to acetic acid, are basophilic and stain by the Ziehl-Neelsen technic. Buña applied the Ziehl-Neelsen method of staining to sections of human and pig tissue, fixed in 10 per cent solution of formaldehyde and embedded in paraffin, and demonstrated that the granules of the eosinophils are not only acid fast but also alcohol fast. The acid-fastness is a relative quality, since the granules are decolorized by prolonged treatment with nitric acid in a dilution of 1:3. He found varying degrees of acid-fastness in the granules of eosinophils, as well as in several other tissue elements. This gradient of acid-fastness he considers quite different from the sharp distinction between the A and A′ granules of Liebereich. Buña also studied the chemical composition of the eosinophil granules by means of microincineration and found that they do not contain iron.

Dark field illumination in the study of stained blood possesses two chief advantages over the bright field technic, according to Ralph.[555] In the first place, structures which otherwise are not seen are rendered visible and resolvable, and, in the second, greater ranges of size, refractivity and color are obtained, permitting a more detailed differentiation of cell types.

A method for determining blood volume in dogs with the aid of radioactive phosphorus is described by Brown, Hempelmann and Elman.[556] In principle it is the same as that employing radioactive iron, but it possesses technical advantages. The authors enumerate the superiorities of cell over plasma methods of determining blood volume, namely: Plasma is not so delimited anatomically as cells; changes in vascular permeability may affect results when plasma is measured; dyes introduced into the blood stream may diffuse out of the plasma or may be excreted. Chapin and Ross [557] believe that the hematocrit method of determining cell volume gives values which are too high. They state that the true cell volume may be determined by dilution of dye T 1824 or by dilution of plasma proteins. Values obtained in this way consistently average 8.5 per cent lower than hemato-

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crit values for cell volume. Results obtained by the use of radioactive iron–tagged erythrocytes agreed with those secured by the dye and plasma protein dilution methods.

Sternal marrow obtained by aspiration may yield cultures of typhoid bacilli when both blood and fecal cultures are negative, according to Sprenger.[558] Twelve cases are reported. The author states that positive results from culture of sternal marrow are not limited to any special period of the illness.

The anemia of flexed tail mice is due to the inheritance of a recessive gene, and the anemia itself conditions the associated skeletal and developmental changes, according to Gruneberg.[559] He describes the anemia as of normocytic, hypochromic type, but the data suggest that macrocytosis persists for a longer period after birth in the anemic mice than in the healthy controls. The author states that pathologic cell development is confined to the early embryonic and extramedullary mode of hemopoiesis. This type of blood cell formation is the sole form of hemopoiesis until the sixteenth day of gestation, and normally it is replaced by the definitive medullary type of erythropoiesis at the time of birth or soon thereafter, but in the anemic mice it persists for about two weeks after birth and ceases by the beginning of the third week. The pathologic erythrocytes formed in this persistent abnormal hemopoiesis survive in the circulation for at least two but not for longer than six weeks. With their final disappearance, the red cell picture of the flexed tail mice becomes entirely normal, but during the transition period between the two modes of erythropoiesis cells of intermediate grades of abnormality are observed in the circulating blood.

The factors governing the sedimentation of erythrocytes have been made the subject of an extensive study, reported in a series of articles, by Nichols.[560] The work includes a survey of the literature on the subject, with a bibliography of 347 references. For his own determinations the author employed horse blood, the Wintrobe tube, Heller and Paul's dry oxalate mixture as an anticoagulant and a photographic recording device.

According to Whittington and Miller,[561] the sedimentation velocity is mainly a function of the agglutination power of the plasma, and the kinematic viscosity of the plasma acts as an extremely sensitive index of its agglutinating power. Therefore, the determination of the viscosity and the specific gravity of the plasma should give information which is analogous to that provided by the measurement of the sedimentation rate. The mathematical concepts which enter into these relationships are discussed, and experimental studies are reported.

The phenomenon of erythrocyte sedimentation is reviewed by Della Vida,[562] who advocates that the test be performed within four hours after the blood has been obtained and that the dry ammonium and potassium oxalate mixture of Heller and Paul be used as an anticoagulant. He prefers a tube 200 mm. in length with a diameter of 2.5 mm. and states that only the rate of fall during the

558. Sprenger, K.: Die sternal Punktion als diagnostisches Hilfsmittel beim Typhus abdominalis, Klin. Wchnschr. **20**:284, 1941.

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period of constant settling should be recorded. Corrections for anemia are made by the use of the "sedimentin index" of Day.

Kopp [563] found no absolute correlation between the plasma concentration of fibrinogen or albumin, the albumin-globulin ratio or the globulin-fibrinogen ratio, on the one hand, and the corrected sedimentation rate, on the other. The sedimentation rate was usually increased when the globulin fraction of the plasma was elevated, regardless of the content of fibrinogen. The author's studies were carried out on 5 male patients undergoing fever therapy for dementia paralytica. He employed the Rourke and Ernstene method of determining the sedimentation rate. The electrophoretic patterns and the sedimentation rates of normal and of pathologic bloods were compared by Shedlovsky and Scudder,[564] who obtained a correlation between the alpha globulin level and the sedimentation rate that was at least as good as the correlation involving the fibrinogen level.

The sedimentation rates of healthy young persons between 11 and 17 years of age are reported by Roche, Stannus and Isberg.[565] The subjects comprised 60 boys and 40 girls, all residents of Miami Beach, Fla. The Rourke and Ernstene method was employed, and the values of 75 per cent of the subjects ranged between 0.09 and 0.65 mm.

The return of the sedimentation rate to normal closely paralleled the clinical recovery from acute glomerulonephritis and could be correlated with changes in the Addis count, according to Rubin, Rapoport and Waltz.[566] Hertz, Ringler and Bernstein [567] were unable to confirm the conclusion of Koster and of Feldman that blood from patients with cancer exhibits an acceleration of sedimentation which persists for twenty-four hours or longer after its withdrawal. They conclude that this test is of no value in the differentation of cancerous from noncancerous conditions.

Teleroentgenograms were made in 32 cases of severe anemia by Gupta.[568] In all but 2 cases there was some increase in the transverse diameter of the heart above the predicted normal. An inverse relation occurred between the hemoglobin content and the cardiac enlargement, but the greatest hypertrophy was found in cases of "hyperchromic" anemia. With improvement of the anemia, a regression of the size of the heart occurred in 95 per cent, although a certain amount of enlargement persisted even after the anemia had been corrected.

Choked disks were observed by Watkins, Wagener and Brown [569] in 4 patients with various types of blood dyscrasia in whom no evidence of a related intracranial lesion was found. Two had thrombopenia purpura. One had severe anemia following recurrent hemorrhage from a gastric ulcer. It was suggested that the papilledema was produced in these instances by local tissue anoxia due to loss of blood.

563. Kopp, I.: The Relationship of the Plasma Proteins to the Corrected Sedimentation Rate, J. Lab. & Clin. Med. **27**:1072, 1942.

564. Shedlovsky, T., and Scudder, J.: A Comparison of Erythrocyte Sedimentation Rates and Electrophoretic Patterns of Normal and Pathological Human Blood, J. Exper. Med. **75**:119, 1942.

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Book Reviews

A Guide to Practical Nutrition. Edited by Michael G. Wohl, M.D., and John H. Willard, M.D., for the Committee on Nutrition and Deficiency Diseases. Price, not given. Pp. 98. Philadelphia: Philadelphia Medical Society, 1943.

These brief articles summarize well current views on nutrition. They are pleasantly written by men who know the subject, some of national reputation. One wonders, however, whether there is really need for so many books on food and vitamins. The subject has been publicized from every possible quarter; lay and professional literature is readily available. There are ponderous treatises, as well as the kindergarten type of syllabus for the ordinary citizen, who (it is presumed) needs a childish approach.

It would seem reasonable in times like these, when economy is important, that additional books on nutrition should contribute something really new. This is hardly the case with the present compendium.

News and Comment

GENERAL NEWS

Mississippi Valley Medical Society.—The ninth annual meeting of the Mississippi Valley Medical Society will be held at Quincy, Ill., September 29 and 30. The program for the meeting will be practical and will be keyed to wartime medicine. All ethical physicians are invited to attend. Medical officers of the Army and Navy are cordially invited to be guests of the society if they register in service uniform. A detailed program of the meeting may be obtained from the secretary, Dr. Harold Swanberg, 209-224 W. C. U. Building, Quincy, Ill.

Mississippi Valley Medical Editors' Association.—No further meetings of the Mississippi Valley Medical Editors' Association will be held for the duration of the war.